Kidney

Renal Stones Revisited - 1984

Charles Y.C. Pak

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The last time a medical grand round was devoted to nephrolithiasis was in 1972.[1] At that time, the substantive progress made from active research which began five years before was reviewed. Using a semiempirical approach based on calculation of activity products,[2] the urinary environment of patients with calcium stones was shown to be supersaturated with respect to brushite ($CaHPO_4 \cdot 2H_2O$). Evidence was presented showing that this mineral constituent could serve as a "precursor phase" for stones of hydroxyapatite and calcium oxalate, principal constituents in stones.[3] Employing an inpatient diagnostic protocol, the syndrome of idiopathic hypercalciuria was shown to result usually from a primary intestinal hyperabsorption of calcium.[4] Sodium cellulose phoshpate, by binding calcium in the intestinal tract, was found to restore normal urinary calcium and saturation of brushite and to inhibit new stone formation.[5]

However, no reliable techniques for the analysis of urinary oxalate, saturation of calcium oxalate, and inhibitor activity applicable to whole urine were available. Thus, formation of the most common type of stones (calcium oxalate) could not be quantitated. Primary hyperparathyroidism and idiopathic hypercalciuria were the only metabolic causes of calcium nephrolithiasis disclosed.[4] Despite an extensive inpatient evaluation, 40% of patients were considered to have "normocalciuric nephrolithiasis" without metabolic abnormality. Orthophosphate and thiazide were the only other medical treatments reported to be useful in calcium nephrolithiasis.

During the past 12 years, the progress in stone research has virtually eliminated the above problems. Physicochemical characterization for stone-forming potential for both stones of calcium phosphate and calcium oxalate is now possible from combined assessment of saturation and inhibitor activity.[6] Metabolic causes have been identified in all but 5% of patients with stones, using an ambulatory protocol.[7] Recurrent nephrolithiasis can now be prevented in the majority of patients employing a variety of selective treatment programs.[8] Recent introduction of innovative techniques for stone removal,[9] via percutaneous approach or extracorporeal shock wave lithotripsy, has further emphasized the need for diagnostic evaluation and selective treatment.

It is the purpose of this medical grand round to review this progress (Fig. 1).

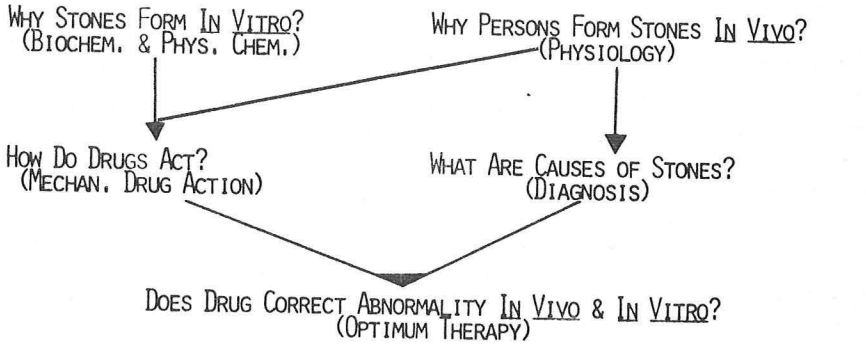


FIGURE 1. Four approaches in urolithiasis research.

Our own approach to nephrolithiasis research has been four-fold. First, we sought physicochemical and biochemical properties of the urinary environment that predisposed to formation of stones. Second, we searched for metabolic defects or physiological derangements that might be etiologically important in patients with stones. Third, the mechanism of action of various therapeutic modalities was elucidated from the ability of these modalities to correct physicochemical abnormalities in the urine and physiological derangements in patients with stones. Fourth, the physiological elucidation has led to the development of improved diagnostic criteria based on underlying metabolic defects. The ultimate goal has always been the formulation of selective treatment approach, where a treatment is specifically chosen according to its ability to correct the underlying physicochemical and physiological disturbances.

We shall briefly review physical chemistry of stone formation in order to provide an appropriate background for the understanding of drug action. We shall place a greater emphasis on the physiological factors leading to stone formation, and on the diagnostic criteria. The remaining time will be devoted to the consideration of selective therapy.

Physical Chemistry of Stone Formation

The current scheme for stone formation, based on physicochemical principles, considers stone formation to begin by nucleation of the crystal nidus, followed by growth of the nidus into a stone through processes of crystal growth, epitaxial growth and crystal aggregation.[10] Nucleation describes the process by which a crystal nidus is formed. Crystal growth represents deposition over the nidus of material of homologous composition, whereas epitaxy indicates growth of heterologous material. Crystal aggregation refers to the process by which preformed crystals aggregate into large clusters.

According to this scheme, stone formation would be promoted when the urinary environment is supersaturated with respect to stone-forming salts and when the inhibitor activity against nucleation, crystal growth, epitaxy or aggregation is reduced. Conversely, stone formation would be impeded by treatments which reduce saturation or augment the inhibitor activity.

Techniques are now available to quantitate these steps in stone formation and prevention. Thus, there is convincing evidence that the urinary environment of patients with stones is conducive to stone formation. First, supersaturation of urine with respect to brushite and calcium oxalate has been invariably found in patients with calcareous calculi,[6] with respect to magnesium ammonium phosphate in those with infection stones,[11] and with respect to cystine in those with cystine stones.[12] Second, the formation product ratio (limit of metastability) of brushite and calcium oxalate is low in the urine of patients with calcium stones, suggestive of reduced inhibitor activity against spontaneous nucleation.[6] Third, the crystal aggregation of calcium oxalate is facilitated in the urine of patients with idiopathic calcium nephrolithiasis.[13] It is believed that urinary supersaturation is the result of an alteration in urinary composition (e.g. hypercalciuria, hyperuricosuria, hyperoxaluria), whereas the reduced inhibitor activity results from deficiency of inhibitors (citrate, pyrophosphate, and organic macromolecules).

Conversely, various treatments have been shown to reduce urinary activity product ratio (saturation), augment formation product ratio[15] or inhibit crystal aggregation (see under "Rational" Therapy).

Elucidation of Physiological Derangements

A simple and logical method of diagnostic differentiation of nephrolithiasis is the categorization on the basis of underlying physiological abnormalities (Table 1). This classification assumes that these physiological disturbances are pathogenetically important in stone formation.

Calcareous stones (calcium oxalate, calcium phosphate) are much more common (>80%) than non-calcareous stones. Causes of calcareous stones include hypercalciuria, hyperuricosuria, hyperoxaluria and hypocitraturia. Hypercalciuria and hyperoxaluria contribute to stone formation by rendering urine supersaturated with respect to stone-forming calcium salts.[2,14] Hyperuricosuria in the setting of normal urinary pH (>5.5) has been associated with calcium nephrolithiasis.[16] It has been suggested that either a colloidal or crystalline monosodium urate forms from such an environment, and initiates formation of calcium oxalate by direct induction of heterogeneous nucleation of calcium oxalate, or by adsorption of certain macromolecular inhibitors.[17-20] The pathogenetic role of hypocitraturia in nephrolithiasis may be ascribed to the inhibitor activity of citrate. Citrate lowers urinary saturation of calcium oxalate by forming a soluble complex with calcium and lowering calcium activity.[21] Moreover, citrate may inhibit crystal growth of calcium oxalate and calcium phosphate.[22]

Among non-calcareous stones, the passage of an unusually acid urine (pH <5.5) would favor the formation of uric acid stones, because of reduced uric acid solubility in such an environment.[17] Although cystine solubility is greater at a higher pH and is enhanced by electrolytes and macromolecules,[12] it rarely exceeds 400 mg/liter. Patients with cystinuria may form cystine stones when their urinary cystine concentration exceeds the solubility limit. In the presence of infection of the urinary tract with urea-splitting organisms, the resulting increase in ammonium ions and alkalinity may lead to struvite (magnesium ammonium phosphate) stone formation.[11]

The physiological background for the various causes of nephrolithiasis will now be discussed.

Pathophysiology of hypercalciurias

Despite recent progress made in the pathogenesis of hypercalciuria, the exact cause for the hypercalciuria associated with nephrolithiasis continues to be debated. The association of hypercalciuria with recurrent calcium nephrolithiasis has long been recognized. The term idiopathic hypercalciuria has been used to denote this entity.[23] One prevailing theory considers idiopathic hypercalciuria to be comprised of several entities of separate pathogenetic origin.[24] On the other hand, a unifying theory assumes that the various forms of hypercalciuria result ultimately from the same generalized defect. In order to provide appropriate background, basic schemes for various forms of hypercalciuria will be described first (Fig. 2).

Table 1. Classification of Nephrolithiasis

Calcareous renal calculi	
Hypercalciuria (40-75%)[a]	
Resorptive	
Absorptive	
Renal	
Hyperuricosuria (∿10%, pure; 30-50% mixed)	
Hyperoxaluria (<5%)	
Primary	
Secondary	
Hypocitraturia (∿5% pure; 10-50% mixed)	
Renal Tubular Acidosis	
Other	
Non-calcareous renal calculi	
Low urinary pH	
Uric acid stones (5%)	
Cystinuria	
Cystine stones (1-3%)	
Infection with urea-splitting organisms	
Struvite stones (15-20%)	

[a], expressed as percentage of total.

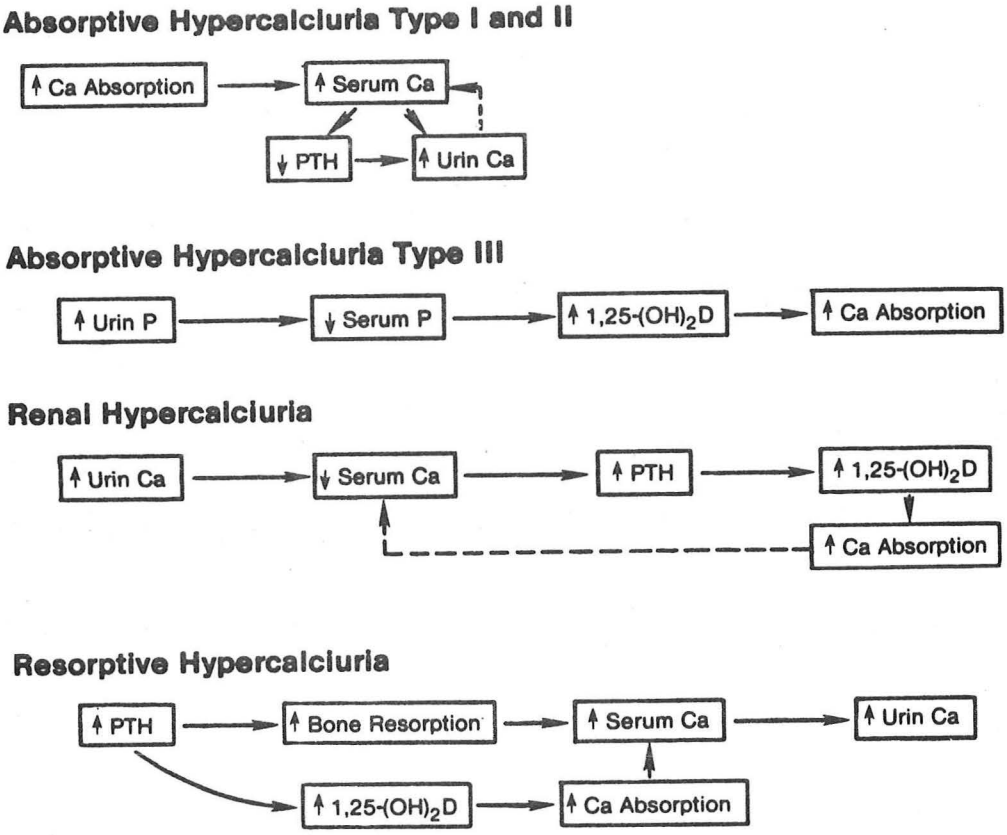


Figure 2. Pathophysiologic schemes for the various forms of hypercalciuria associated with nephrolithiasis.

Absorptive hypercalciuria. In absorptive hypercalciuria, the principal abnormality is the intestinal hyperabsorption of calcium.[24] The consequent increase in the circulating concentration of calcium augments the renal filtered load and suppresses parathyroid function. Hypercalciuria ensues from the increased renal filtered load and the reduced tubular reabsorption of calcium consequent to parathyroid suppression. The excessive renal loss of calcium compensates for the high calcium absorption from the intestinal tract and helps to maintain serum calcium in the normal range.

Absorptive hypercalciuria occurs in several forms.[25] In one form (absorptive hypercalciuria Type I), elevated urinary calcium is found during both low and high calcium intakes, whereas in another form (absorptive hypercalciuria Type II), it is encountered only during a high calcium intake. The Type II presentation is a less severe form of Type I. Both forms may occur in the same patient during the course of the disease.

The third type of absorptive hypercalciuria, absorptive hypercalciuria Type III, implicates a renal "leak" of phosphate as the primary event.[26] The ensuing hypophosphatemia is then believed to stimulate the renal synthesis of 1,25-dihydroxyvitamin D (1,25-$(OH)_2$D). The enhanced intestinal absorption and renal excretion of calcium would result from the increased synthesis of the vitamin D metabolite.

Renal hypercalciuria. The primary abnormality in renal hypercalciuria is believed to be the impairment in the renal tubular reabsorption of calcium.[27-29] The consequent reduction in the circulating concentration of calcium stimulates parathyroid function. There may be an excessive

Table 2. Evidence That Absorptive and Renal Hypercalciurias Are Physiologically Distinct

Item	Absorptive Hypercalciuria Type I or Type II	Renal Hypercalciuria
Parathyroid function	Normal or suppressed	Stimulated
Renal calcium leak	Secondary	Primary
Effect of sodium cellulose phosphate	Correctable	Non-correctable
Natriuretic response to thiazide	Normal	Exaggerated
Intestinal calcium absorption	Primarily increased	Secondarily increased
Jejunal absorption	Increased	Increased
Ileal absorption	Normal	Increased
Intestinal magnesium absorption	Normal	Increased
Serum 1,25-$(OH)_2D$ vs. calcium absorption	No correlation	Correlated
Effect of treatment		
Thiazide		
Serum 1,25-$(OH)_2D$ and Calcium absorption	No change	Decreased
Sodium cellulose phosphate		
Urinary calcium	Markedly decreased	Less marked
Calcium conservation	Intact	Impaired
Skeletal status		
Bone density	Normal	Decreased
Calcium balance	Normal	Normal or negative

mobilization of calcium from bone and an enhanced intestinal absorption of calcium from the parathyroid hormone (PTH)-excess and the ensuing stimulation of the renal synthesis of $1,25\text{-}(OH)_2D$. These effects restore serum calcium toward normal. Unlike in primary hyperparathyroidism, serum calcium is normal and the state of hyperparathyroidism is secondary.

Resorptive hypercalciuria. In resorptive hypercalciuria, characterized by primary hyperparathyroidism, the initial event is the excessive resorption of bone resulting from the hypersecretion of PTH. The intestinal absorption of calcium is frequently elevated, because of the PTH-dependent stimulation of the renal synthesis of $1,25\text{-}(OH)_2D$.[30,31] These effects increase the circulating concentration and the renal filtered load of calcium. The occurrence of hypercalciuria in primary hyperparathyroidism seems paradoxical, since the primary renal effect of PTH is to stimulate the tubular reabsorption of calcium. However, hypercalciuria is often encountered in primary hyperparathyroidism because the PTH-dependent augmentation of renal tubular reabsorption of calcium is "overcome" by an increase in the renal filtered load and by a suppressive effect of hypercalcemia on calcium reabsorption.

Evidence for separate etiologies of absorptive and renal hypercalciurias

Six lines of evidence suggest that absorptive hypercalciuria (Type I and II with normal serum phosphorus) and renal hypercalciuria are separate and distinct entities[27] (Table 2).

Parathyroid function. First, parathyroid function should be normal or suppressed in absorptive hypercalciuria, and stimulated in renal hypercalciuria.

In absorptive hypercalciuria, numerous studies have shown normal serum immunoreactive PTH and urinary cyclic AMP. Following an oral calcium load, urinary cyclic AMP is significantly lower in absorptive hypercalciuria than in control subjects, probably because the larger amount of calcium absorbed in the former group has suppressed parathyroid function to a greater degree.[32]

In renal hypercalciuria, high serum PTH and urinary cyclic AMP have been reported in several studies (Table 3). These disturbances may be corrected by oral calcium load or thiazides, emphasizing that parathyroid function is secondarily stimulated.

Table 3. Parathyroid Function in Hypercalciuria

Author	Percentage of Patients with Hypercalciuria	
	Renal Hypercalciuria + Parathyroid Stimulation	Fasting Hypercalciuria + Normal Parathyroid Function
Elomaa et al.	10	0
Bataille et al.	13	19
Kraism et al.	31	31
Sutton and Walker	0	60
Coe et al.	0	59
Pak and Zerwekh	9	13

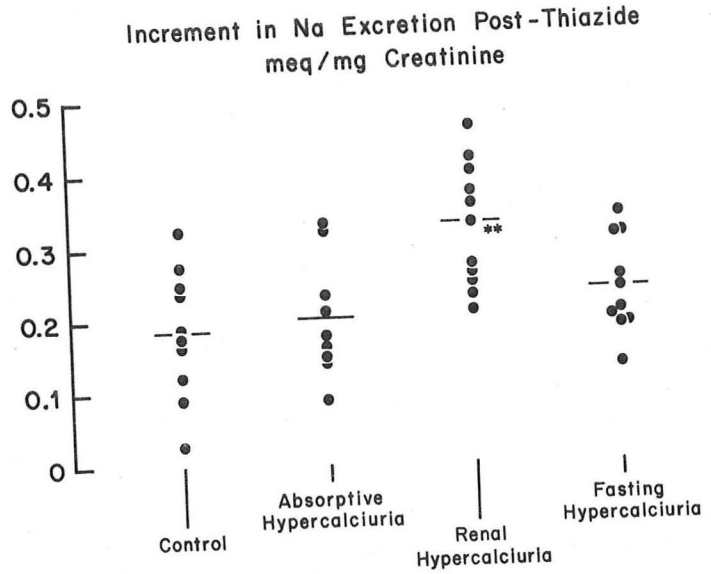
Renal calcium leak. Second, there should be evidence for a primary renal calcium leak in renal hypercalciuria, but not in absorptive hypercalciuria. The presence of a renal leak of calcium may be detected from the high fasting urinary calcium. If the duration of fast is sufficient, the absorbed calcium (from the intestinal tract) provides a limited contribution to urinary calcium. In normocalcemic patients, in whom the renal filtered load of calcium probably is not increased, a high fasting urinary calcium indicates that a renal leak of calcium may be present.[32] A high fasting urinary calcium has been found to be invariably present in patients with renal hypercalciuria in whom the diagnosis was reached independently. In contrast, urinary calcium during fasting was shown to be usually within the normal range in patients with absorptive hypercalciuria, provided that the absorbed calcium had been cleared by the kidneys.[33] These results suggested that the renal tubular reabsorption of calcium may be impaired in renal hypercalciuria but not in absorptive hypercalciuria.

It has been suggested that a renal leak of calcium may have occurred secondarily from an exaggerated sodium intake.[34] Indeed, a sustained high intake of sodium in normal subjects has been shown to produce the picture of renal hypercalciuria, including hypercalciuria, high serum $1,25\text{-}(OH)_2D$ and enhanced intestinal absorption of calcium.[35] However, this contention is unlikely for the following reasons.

In patients with renal hypercalciuria, fasting hypercalciuria was found while they were maintained or instructed to remain on the same sodium intake (100 meq/day) as in control subjects.[7] Twenty-four hour urinary sodium in renal hypercalciuria of 141±66 SD meq/day was not significantly different from the value in control subjects of 106±46 meq/day. Even though the mean sodium excretion was higher in renal hypercalciuria by 35 meq/day, this amount of sodium intake does not substantially increase the renal excretion of calcium. An exaggerated sodium load (250 meq/day for 10 days) following a low sodium intake (9 meq/day) caused a small but significant increase in fasting urinary calcium in normal subjects; however, fasting urinary calcium remained within normal limits (unpublished observations). Finally, no significant difference was found between fasting urinary sodium among control subjects and patients with absorptive hypercalciuria.[7]

That a proximal tubular dysfunction is present and confined to renal hypercalciuria is further supported by response to thiazide treatment. In a preliminary study, an exaggerated natriuretic response to hydrochlorothiazide was encountered in renal hypercalciuria, but not in absorptive hypercalciuria or in fasting hypercalciuria with normal parathyroid function (Fig. 3).[36]

Fig. 3.



In some patients with absorptive hypercalciuria, fasting urinary calcium may be increased.[33] This finding need not indicate that renal calcium handling is primarily affected, since it may reflect an incomplete clearance of absorbed calcium, or a renal leak of calcium occurring secondarily from parathyroid suppression.

Normally, there is an inverse relationship between fasting urinary calcium and cyclic AMP. This relationship may have physiologic relevance, since it may reflect the effect of varying degrees of absorbed calcium remaining in circulation on parathyroid function. Thus, an incomplete clearance of excessively absorbed calcium would lead to a higher value for fasting urinary calcium, and a lower value for cyclic AMP (since some of the absorbed calcium would be left in circulation to suppress parathyroid function). Most of the values in absorptive hypercalciuria were shown to be within 2 standard errors of the estimate describing this relationship for control subjects, whereas values in renal hypercalciuria were above this limit. Discriminant analysis allowed derivation of fasting urinary calcium-cyclic AMP discriminant score, which gave a much better separation between absorptive and renal hypercalciurias than was possible from fasting urinary calcium or cyclic AMP used alone.[33] Positive scores were characteristic of renal hypercalciuria and negative scores of absorptive hypercalciuria.

The effect of sodium cellulose phosphate therapy on fasting urinary calcium-cyclic AMP discriminant score helped to determine whether the renal leak of calcium was primary or secondary. In absorptive hypercalciuria, values before treatment with sodium cellulose phosphate were located on the left part of this regression, toward higher fasting urinary calcium and lower cyclic AMP (Fig. 4).[27] In a minority of patients, fasting urinary calcium was increased. Following sodium cellulose phosphate therapy (with more complete removal of absorbed calcium), values were shifted to the right of the regression line defined for the normal group. Thus, both fasting urinary calcium and cyclic AMP remained or became normal. The finding indicated that the high fasting urinary calcium encountered in some

patients with absorptive hypercalciuria resulted from an incomplete clearance of absorbed calcium. Alternatively, the results suggest that the renal leak of calcium acquired from parathyroid suppression was corrected by a restriciton of normal parathyroid function from a more complete removal of absorbed calcium.

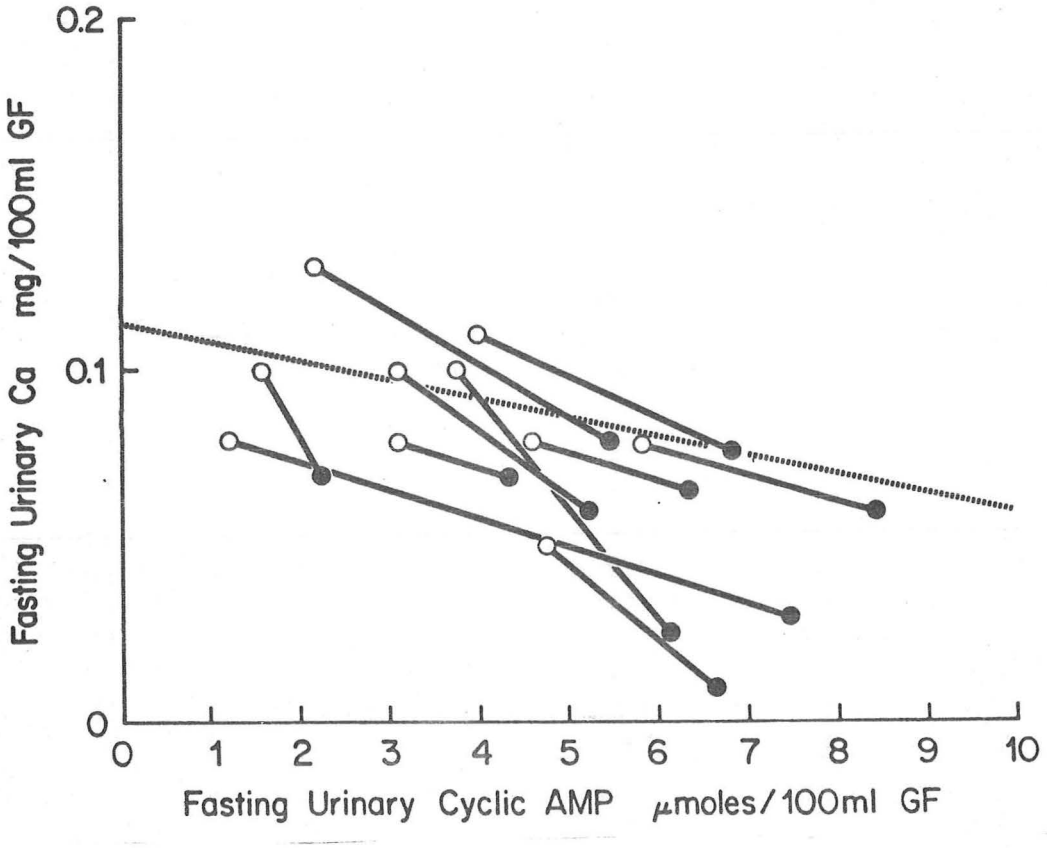


Figure 4. Effect of sodium cellulose phosphate (SCP) treatment on fasting urinary calcium and cyclic AMP in patients with absorptive hypercalciuria. The dashed diagonal line indicates mean + 2 standard error of estimate for values in control subjects. Open circles indicate pre-treatment, and closed circles treatment values.

In contrast, values in renal hypercalciuria remained outside the regression line defined for normal subjects following treatment with sodium cellulose phosphate. The results indicated that a more complete removal of absorbed calcium had further stimulated parathyroid function without completely correcting renal calcium leak.

Intestinal calcium absorption. Third, intestinal calcium absorption is invariably increased in absorptive hypercalciuria, but not always in renal hypercalciuria.[27] In absorptive hypercalciuria, hypercalciuria probably occurs secondarily from the enhanced calcium absorption, since the absorbed calcium typically exceeds urinary calcium (the difference being accountable by net secreted calcium).[24] The difference between absorbed calcium and urinary calcium has been shown to be somewhat lower in patients

with absorptive hypercalciuria than in control subjects. This finding need not indicate that calcium balance was negative, since it could reflect increased absorption of secreted calcium by patients with absorptive hypercalciuria. Although some patients with idiopathic hypercalciuria have been shown to have negative calcium balance,[37] they may not have suffered from absorptive hypercalciuria. Moreover, the results of calcium balance studies should be interpreted with caution because of relative imprecise-ness of balance techniques.[38]

In contrast, the intestinal calcium absorption is increased in some but not all patients with renal hypercalciuria. The results suggest that the increased calcium absorption of renal hypercalciuria may not represent a primary derangement, but probably indicates a secondary event. The absorbed calcium is often less than the urinary calcium.

Vitamin D metabolism. Fourth, there is apparently a varying role of vitamin D metabolism. In renal hypercalciuria, the fractional calcium absorption was found to be directly correlated with the circulating concentration of 1,25-$(OH)_2$D.[27] Accordingly, the probable scheme for the increased calcium absorption is: renal leak of calcium → stimulation of PTH secretion → enhanced renal synthesis of 1,25-$(OH)_2$D → increased calcium absorption. The validity of this hypothesis was shown by the restoration of normal serum 1,25-$(OH)_2$D and intestinal calcium absorption following the correction of renal calcium leak with thiazide therapy.[29]

In absorptive hypercalciuria, a similar dependence on 1,25-$(OH)_2$D cannot be invoked.[30] The fractional calcium absorption was not correlated with serum 1,25-$(OH)_2$D. In most patients, the fractional calcium absorption was inappropriately high for the level of serum 1,25-$(OH)_2$D.

Studies of intestinal perfusion provided a further insight in the potential pathogenetic role of vitamin D in absorptive hypercalciuria. Calcium absorption was found to be increased in jejunum but normal in ileum (Fig. 5).[39] Magnesium absorption in jejunum was normal.[40] The increased calcium absorption in jejunum was not attenuated by magnesium.[27] This transport profile differs from the vitamin D action. The treatment with 1,25-$(OH)_2$D of patients with renal failure and normal subjects has been shown to augment calcium absorption in both intestinal segments, as well as enhance magnesium absorption.[41,42] Moreover, the hyperabsorption of calcium may not be corrected by treatment with adrenocorticosteroids,[43] thiazides[29] or orthophosphate,[44] even though orthophosphate treatment reduces the serum concentration of 1,25-$(OH)_2$D.

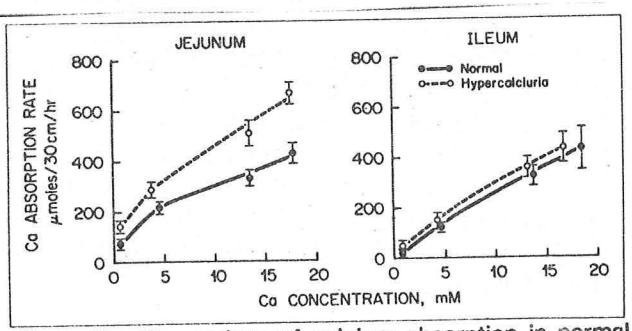


Figure 5. Comparison of calcium absorption in normal subjects and in patients with absorptive hypercalciuria (AH) at different luminal concentrations of calcium in the jejunum and in the ileum. Calcium concentration refers to the luminal calcium concentration, that is, the arithmetic mean of calcium contents in the luminal fluid of the proximal and distal collecting sites. The values for luminal calcium were slightly less than the corresponding perfusate concentrations.

Response to treatment. Fifth, absorptive hypercalciuria and renal hypercalciuria may be differentiated from each other on the basis of their unique responses to certain treatments.

In renal hypercalciuria, thiazide therapy "corrected" the renal calcium leak and restored normal parathyroid function, serum 1,25-$(OH)_2D$ concentration, and fractional calcium absorption.[29] In absorptive hypercalciuria, however, the serum concentration of 1,25-$(OH)_2D$ remained unchanged and the intestinal hyperabsorption of calcium persisted despite a reduction in urinary calcium.[27-29]

An inhibition of intestinal calcium absorption by sodium cellulose phosphate caused a less prominent reduction in urinary calcium in renal hypercalciuria than in absorptive hypercalciuria.[45] Moreover, it caused an exaggeration of secondary hyperparathyroidism in renal hypercalciuria.[33]

In absorptive hypercalciuria, the decline in urinary calcium during cellulose phosphate treatment could be accounted by the inhibition of calcium absorption, since the absorbed calcium during treatment exceeded urinary calcium (unpublished observation). Moreover, sodium cellulose phosphate treatment did not significantly affect calcium balance, serum alkaline phosphatase, urinary hydroxyproline or radial bone density, and maintained parathyroid function within the normal range. The results suggested that there is adequate calcium conservation during therapy with sodium cellulose phosphate.

Sequelae of PTH excess. Sixth, there is evidence for deleterious sequelae of PTH excess in renal hypercalciuria, but not in absorptive hypercalciuria. Although clinical bone disease is rare, quantitative measurement of bone density by photon absorptiometry has disclosed a significant reduction in the group with renal hypercalciuria (compared with age- and sex-matched control group).[46] The results indicated that secondary hyperparathyroidism had exerted deleterious effects on the skeleton. The lack of a more substantial involvement was probably due to the compensatory intestinal hyperabsorption of calcium occurring from the PTH-induced renal synthesis of 1,25-$(OH)_2D$.

In contrast, bone density was not significantly different from the control group in absorptive hypercalciuria.[46] Moreover, patients with absorptive hypercalciuria had normal serum alkaline phosphatase, gamma-carboxyglutamic acid (gla)-containing protein and urinary hydroxyproline, findings suggesting that osteoblastic formation and osteoclastic resorption were not grossly disturbed (unpublished observations). The results indicated intact skeletal status in absorptive hypercalciuria.

In summary, that absorptive hypercalciuria (Type I or Type II) is intestinal and not renal in origin is suggested by: (a) the high intestinal calcium absorption which exceeds urinary calcium, (b) normal/suppressed parathyroid function, (c) lack of evidence for a disturbance in renal proximal tubular function, indicated by normal fasting urinary calcium, serum phosphorus and natriuretic response to thiazide, (d) selective intestinal hyperabsorption for calcium (not magnesium) in jejunum (not ileum), patterns atypical for 1,25-$(OH)_2D$ action and hyperparathyroid states, (e) inappropriately low serum 1,25-$(OH)_2D$ for the level of intestinal calcium absorption, and a lack of correlation between

intestinal calcium absorption and serum 1,25-$(OH)_2D$, (f) inability of treatment by adrenocorticosteroids, thiazide, or orthophosphate, to entirely correct the hyperabsorption of calcium, (g) intact skeletal status, shown by normal serum alkaline phosphatase, gla-containing protein, urinary hydroxyproline, and bone density, and (h) adequate calcium conservation during inhibition of intestinal calcium absorption by treatment with sodium cellulose phosphate.

There is also sufficient evidence for the existence of renal hypercalciuria of primary renal origin with secondary hyperparathyroidism (Table 3). It is characterized by normocalcemia, high fasting urinary calcium (indicative of renal calcium leak), high serum PTH and/or urinary cyclic AMP (suggestive or parathyroid stimulation), high serum concentration of 1,25-$(OH)_2D$ which is positively correlated with intestinal calcium absorption (indicating compensatory intestinal hyperabsorption of calcium from the PTH-induced stimulation of 1,25-$(OH)_2D$ synthesis), and restoration by thiazide treatment of normal fasting urinary calcium, parathyroid function, serum 1,25-$(OH)_2D$ and calcium absorption (suggesting disturbances are secondary to renal calcium leak). That parathyroid stimulation may have exerted a deleterious effect is shown by reduced bone density detected with photon absorptiometry, despite rarity of clinical bone disease. It should be noted that the diagnosis of renal hypercalciuria requires the demonstration of parathyroid stimulation.

Difficulty with separative theory of hypercalciurias

A major problem is the occurrence of fasting hypercacliuria without parathyroid stimulation in normocalcemic patients with hypercalciuric nephrolithiasis.[47] This picture depicts neither absorptive hypercalciuria nor renal hypercalciuria. The lack of hyperparathyroidism suggests the occurrence of absorptive hypercalciuria, but fasting urinary calcium is high. The fasting hypercalciuria indicates that a renal leak of calcium is present; however, secondary stimulation of parathyroid function is lacking.

The relative proportion of patients with fasting hypercalciuria without parathyroid stimulation in those with hypercalciuric nephrolithiasis varies considerably among available reports (Table 3). Of 241 consecutive patients with stones evaluated in an outpatient setting, 23 patients presented with this picture, compared to 123 with absorptive hypercalciuria and 16 with renal hypercalciuria and secondary hyperparathyroidism.[7]

There are several possibilities for the occurrence of fasting hypercalciuria without parathyroid stimulation.[47] They include: inadequate preparation on a diet restricted in calcium and sodium,[33] relative insensitivity of the PTH assay, excessive skeletal mobilization of calcium and altered set point for PTH release.

Unifying theory of hypercalciurias

Much of the overall features of idiopathic hypercalciuria could be explained by a disturbance in renal proximal tubular function, characterized by varying degrees of calcium leak, a disturbance in phosphate transport and accelerated 1,25-$(OH)_2D$ synthesis (Fig. 6).[48] This unifying scheme could explain the pathogenesis of both renal and absorptive hypercalciurias from the same general defect originating in the kidney. The predominance of the renal calcium leak (route 1) would lead to renal hypercalciuria with secondary hyperparathyroidism. On the other hand, the prominence of

1,25-$(OH)_2D$ synthesis, occurring independently (route 3) or secondarily from renal phosphate leak (route 2), would produce a picture of absorptive hypercalciuria by enhancing intestinal calcium absorption and masking parathyroid stimulation. The occurrence of both renal calcium leak and renal phosphate leak or increased 1,25-$(OH)_2D$ synthesis may produce a picture of fasting hypercalciuria without parathyroid stimulation. Thus, renal hypercalciuria need not be accompanied by hyperparathyroidism, and absorptive hypercalciuria results secondarily from 1,25-$(OH)_2D$-dependent stimulation of intestinal calcium absorption.

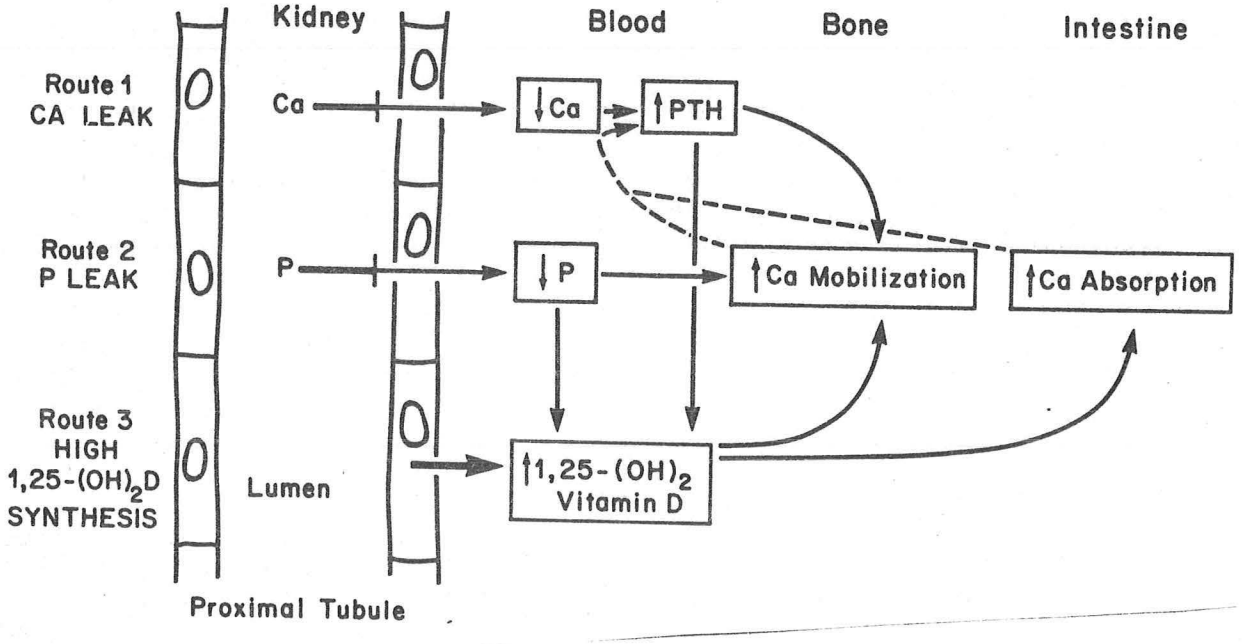


Figure 6. Scheme for the unifying theory of hypercalciurias.

While attractive, this unifying hypothesis is inadequate in accounting for the available data supportive of separate etiologies for the hypercalciurias as described previously. Salient argument against this theory may be recapitulated as follows.

First, intestinal perfusion studies, indicating selective jejunal (not ileal) absorption of calcium (not magnesium) in absorptive hypercalciuria, do not support a 1,25-$(OH)_2D$-dependent process.[39]

Second, if either hypophosphatemia or 1,25-$(OH)_2D$ were exerting a pathogenetic role in absorptive hypercalciuria, it is expected that patients would be in negative calcium balance, that they would have inadequate ability for calcium conservation, and that their skeleton would be adversely affected. However, as described before, there is substantive evidence that skeletal status is intact in absorptive hypercalciuria, and that there is adequate calcium conservation during therapy with sodium cellulose phosphate. The finding of normal fasting urinary calcium, cyclic AMP and discriminant score during sodium cellulose phosphate indicates further that calcium conservation is intact.[33]

Third, the demonstration of urinary calcium exceeding dietary calcium during severe calcium restriction has been engaged in favor of the argu-

ment that calcium conservation is inadequate in absorptive hypercalciuria.[48] Unfortunately, this study was conducted in an outpatient setting with instructed (and not metabolic) diet, and without apparent chemical analysis of the diet. Moreover, serum PTH remained subnormal despite 7 days of "severe" calcium restriction, a finding suggesting the possibility that there was an altered set point for PTH release toward impaired secretion, possibly because of the prolonged suppressive stimulus from increased calcium absorption. Thus, the inadequate conservation could have resulted from an acquired renal calcium leak from parathyroid suppression.

Pathophysiology of other physiological derangements will now be discussed (Table 4).

Pathophysiology of hyperuricosuria

Uric acid is an end-product of purine metabolism. It cannot be degraded further in human beings which lack uricase, unlike in lower mammalian species. The major site of disposal of uric acid is the kidney, where both secretory and reabsorptive processes have been implicated.

Hyperuricosuria may ensue when the serum concentration and the renal filtered load of uric acid are increased from (a) the provision of an excessive amount of substrate (purine), e.g. a high dietary intake of purine-rich foods[49] or an accelerated cellular degradation and release of nucleic acids, or (b) a disturbance in the enzymatic pathway for purine biosynthesis stimulating uric acid synthesis. A high urinary uric acid may be transiently encountered when the renal tubular reabsorption of uric acid is impaired, e.g. during early stages of extracellular volume expansion with sodium load and following administration of uricosuric agents such as probenecid. In late stages, however, normal urinary uric acid is restored, because of the decline in serum concentration and renal filtered load of uric acid, even though the renal tubular reabsorption of uric acid remains impaired.[50]

Hyperuricosuria may be the only recognizable physiological abnormality in patients with calcium nephrolithiasis. Such an abnormality (hyperuricosuric calcium oxalate nephrolithiasis or hyperuricosuric calcium urolithiasis) exists in approximately 10% of patients with renal calculi.[7] Although hyperuricosuria may coexist with various forms of hypercalciuria previously enumerated, this section will consider the pure presentation.

The cause for the hyperuricosuria in the majority of patients with hyperuricosuric calcium oxalate nephrolithiasis is probably the "dietary overindulgence" with purine-rich foods.[49] They give a history of a liberal intake of meat, poultry and fish. Estimated purine intake is higher than in the control group. Hyperuricosuria may be produced by an oral purine load, and ameliorated by dietary purine deprivation.[18,49]

However, in the minority of patients with hyperuricosuric calcium oxalate nephrolithiasis (approximately 30%), hyperuricosuria may be partly the result of uric acid overproduction. Hyperuricosuria persists despite long-term purine deprivation. No further studies have been performed to elucidate the nature of this apparent urate overproduction.

Pathophysiology of hyperoxaluria

Oxalate is available to human beings by *in vivo* synthesis and by intestinal absorption. Once synthesized or absorbed, it is not further de-

Table 4. Pathophysiologic Schemes for Physiological Derangements Other than Hypercalciuria

Physiological Derangement	Causes
Hyperuricosuria	Primary overproduction Dietary purine overindulgence or increased cellular degradation
Hyperoxaluria	High substrate availability (e.g. vitamin C or oxalate intake Primary overproduction Intestinal hyperabsorption of oxalate (enteric hyperoxaluria)
Hypocitraturia	Renal tubular acidosis Enteric hyperoxaluria Hypokalemia (e.g. thiazide therapy) High animal protein diet Urinary tract infection Other
Low urinary pH (uric acid stones)	Gout and chronic diarrheal syndrome High animal protein diet
Cystinuria	Impaired renal tubular reabsorption of cystine
High urinary pH and ammonium (struvite stones)	Infection with urea-splitting organisms

graded in vivo. Its principal route of excretion is the kidney. Data on renal handling of oxalate are limited and conflicting. Of the 30 mg of oxalate that is excreted normally, 80-90% may be accounted by in vivo synthesis and the remainder by intestinal absorption.

Hyperoxaluria resulting from a primary derangement in the renal handling of oxalate has not been recognized. It typically occurs from the increased serum concentration and renal filtered load of oxalate by (a) high substrate availability, e.g. methoxyflurane and ascorbic acid, (b) enzymatic disturbance(s) in oxalate biosynthetic pathway, as in primary hyperoxaluria (rare), or (c) an increased intestinal absorption of oxalate.

An increased intestinal absorption of oxalate is present and accounts for the hyperoxaluria in ileal disease.[51-53] Two influences probably combine to cause the intestinal hyperabsorption of oxalate. The intestinal transport of oxalate may be primarily increased from the action of bile salts and fatty acids on the permeability of intestinal mucosa to oxalate. The total amount of oxalate absorbed may also be increased because of an enlarged intraluminal pool of oxalate available for absorption. The intestinal fat malabsorption characteristic of ileal disease may exaggerate the soap formation with divalent cations, limit the amount of "free" divalent cations to complex oxalate and thereby raise the available oxalate pool.

In addition to the disturbance in oxalate metabolism, the intestinal absorption and renal excretion of calcium are often decreased in enteric hyperoxaluria, probably reflective of the loss of intestinal site of calcium absorption from disease or resection, of intraluminal binding of calcium by non-absorbed fatty acids, or of vitamin D deficiency associated with fat malabsorption. Urine output may be substantially reduced consequent to fluid loss from the intestinal tract. Urinary citrate may be low because of hypokalemia and metabolic acidosis.[54,55] Low urinary magnesium may result from impaired intestinal magnesium absorption.

The cause for the formation of calcium oxalate stones is multifactorial, and includes hyperoxaluria as well as some of the other disturbances enumerated. There may be an increased saturation of urine with respect to calcium oxalate because of high oxalate concentration, even though urinary calcium may be low. Low urine volume exaggerates urinary supersaturation. Moreover, the inhibitor activity against crystallization of calcium salts is reduced because of low renal excretion of citrate and magnesium.

Pathophysiology of hypocitraturia

Urinary citrate excretion is a function of filtration, reabsorption, peritubular transport, and synthesis by tubular cell.[56] Approximately 80-90% of filtered citrate is normally reabsorbed. Citrate secretion is negligible in man. Peritubular transport (citrate flux between peritubular blood and tubular cell) and tubular synthesis do not directly influence citrate excretion in urine; they do so by affecting renal tissue content of citrate and ultimately the filtered load of citrate.

Although the exact physiology of the renal handling of citrate has not been elucidated, several factors which influence citrate excretion are recognized. Citrate excretion may be enhanced by alkalosis,[57] PTH,[58] vitamin D, growth hormone, and estrogen. On the other hand, citrate excretion may be impaired by acidosis,[59] hypokalemia,[60,61] androgen, and urinary tract infection. Among these factors, the acid-base status pro-

bably plays the most critical role in the renal handling of citrate. For example, the acidotic state reduces urinary citrate by enhancing the renal tubular reabsorption and reducing the synthesis of citrate. This mechanism accounts for the occurrence of hypocitraturia in renal tubular acidosis, enteric hyperoxaluria, hypokalemia (from intracellular acidosis), and high animal protein diet (from elevated acid-ash content).

Among patients with stones, hypocitrauria is invariably found in renal tubular acidosis (complete or incomplete), enteric hyperoxaluria and in urinary tract infection.

It is also often found with other causes of calcium nephrolithiasis (10-50%), and occurs as the sole abnormality (5%), from heretofore unidentified mechanism. Preliminary studies indicated that renal tubular reabsorption of citrate is increased.[62]

Pathophysiology of non-calcareous stones

Critical determinants for uric acid lithiasis are passage of urine with pH less than the dissociation constant for uric acid (5.47) and/or hyperuricosuria.[17] Uric acid lithiasis often occurs in primary gout, which may be accompanied by low urinary pH and hyperuricosuria. Uric acid lithiasis may also be found in secondary causes of purine overproduction, such as myeloproliferative states, glycogen storage disease, and malignancy. Chronic diarrheal syndromes (ulcerative colitis, regional enteritis, jejunoileal bypass surgery) may cause uric acid lithiasis, by inducing net alkali deficit and lowering urine volume (thereby reducing urinary pH and augmenting urinary concentration of uric acid, respectively).

Cystinuria is due to an inborn error of metabolism, characterized by a disturbance in renal and intestinal handling of dicarboxylic acids, including cystine. Stone formation, occurring in a minority of patients with cystinuria, is the result of an excessive renal excretion of cystine and its low solubility in urine.[12]

Infection of the urinary tract with urea-splitting organisms may be associated with renal stones of struvite and of calcium carbonate apatite.[11] The critical determinant is the formation of ammonia in urine upon enzymatic degradation of urea by bacterial urease. The ammonia undergoes hydration to form ammonium and hydroxyl ions. The resulting alkalinity of urine augments dissociation of phosphate to form more triphosphate ions, and reduces the solubility of struvite. Thus, the urinary environment becomes supersaturated with respect to struvite. Although struvite stones may form de novo from infection alone, they may sometimes occur as a complication of other causes of renal calculi, such as hypercalciuria.

Diagnostic Considerations

Reliable protocols are now available for the differentiation of different forms of nephrolithiasis. Our own ambulatory protocol[7] requires three outpatient visits, and may be completed within a month (Table 5). This evaluation depends largely on procedures that should be available in a routine clinical laboratory. Certain specialized procedures may be obtained commercially. It is cost-effective, since it could be conducted at a fraction of the cost incurred during hospitalization for renal colic. Diagnostic criteria for the major forms of nephrolithiasis are summarized in Table 6.

TABLE 5 *Outline of ambulatory protocol*

	Laboratory Tests												
	Blood			Urine									
	Complete Blood Count	SMA	PTH	Calcium	Uric Acid	Creatinine	Sodium	pH	Total Volume	Oxalate	Cyclic AMP	Citrate	Qualitative Cystine
Visit 1*	X	X	X	X	X	X	X	X	X				X
Visit 2†				X	X	X	X	X	X				
Visit 3‡		X		X	X	X	X	X	X	X	X	X	
Fast				X		X							
Load				X		X							

* History and physical examination, 24-hour urine on random diet.
† 24-Hour urine on random diet, diet history and instruction.
‡ 24-Hour urine on restricted diet (400 mg. calcium and 100 mEq. sodium daily), fast and load.

Absorptive hypercalciuria Type I[7] is characterized by normocalcemia, normophosphatemia, normal fasting urinary calcium (<0.11 mg/100 ml glomerular filtrate (GF)),[7] exaggerated urinary calcium following an oral calcium load (>0.2 mg/mg creatinine),[32] normal or suppressed parathyroid function (normal serum immunoreactive PTH and 24-hr urinary cyclic AMP <5.4 nmole/100 ml GF), and urinary calcium on a restricted diet (400 mg calcium and 100 meq sodium/day) of greater than 200 mg/day.[24,47] These values reflect increased intestinal calcium absorption, resultant parathyroid suppression, and hypercalciuria.

Absorptive hypercalciuria Type II is characterized by the same biochemical features as Type I except for normocalciuria (<200 mg/day) on a restricted diet (400 mg calcium and 100 meq sodium/day). Indeed, if these patients are placed on a diet of 1000 mg calcium and 100 meq sodium/day, urinary calcium exceeds 4 mg/kg per day or 250 mg/day.[47] Features of absorptive hypercalciuria Type III are the same as those of Type I presentation, except for hypophosphatemia (<2.5 mg/dl).

Renal hypercalciuria is manifested by normocalcemia, high fasting urinary calcium (>0.11 mg/100 ml GF),[7] and parathyroid stimulation (high serum immunoreactive PTH and/or 24-hr urinary cyclic AMP >5.4 nmole/100 ml GF).[7,24] These results are indicative of a renal leak of calcium with compensatory parathyroid stimulation. It should be noted that either the serum PTH or urinary cyclic AMP (on the restricted 24-hr sample) must be elevated to diagnose renal hypercalciuria. In most patients, urinary cyclic AMP, which is high in the fasting state, decreases to the normal range following an oral calcium load,[32] a finding indicative of the suppressibility of parathyroid stimulation. Bone density may be low in patients with renal hypercalciuria,[46] and in some cases osteopenia may occur.

Primary hyperparathyroidism may be recognized by the presence of hypercalcemia, hypophosphatemia, hypercalciuria, and increased or inappropriately high serum PTH and/or urinary cyclic AMP.[63] The fasting urinary cyclic AMP tends to be high and is not restored to normal following an oral calcium load,[32] a result suggesting relative non-suppressibility of PTH secretion. Hypercalcemic symptoms, peptic ulcer, or bone disease (osteitis, pathological fractures, osteoporosis) may be present.

Hyperuricosuric calcium oxalate nephrolithiasis[16,17] is characterized by hyperuricosuria (urinary uric acid >600 mg/day on mean of three samples and on at least two samples),[7] normocalcemia, normal fast and calcium load response,[32] normal urinary calcium and oxalate (<44 mg/day), and calcium nephrolithiasis. Hyperuricosuria, defined functionally here by the upper normal limit of 600 mg/day, has been found to correlate well with the urinary supersaturation with respect to monosodium urate and with the propensity for calcium stone formation.[17] (Other laboratories employ a higher upper limit for urinary uric acid, e.g., 750 mg/day for women and 800 mg/day for men.) Urinary pH is typically greater

Table 6. Diagnostic Criteria for Hypercalciurias

	PHPT	AH-I	AH-II	AH-III	RH	HUCU	EH
Serum Ca	↑	N	N	N	N	N	N/↓
Serum P	↓/N	N	N	↓	N	N	N/↓
Urinary Ca	↑/N	↑	N	↑/N	↑	N	↓
Serum PTH	↑	N/↓	N/↓	N/↓	↑	N	N/↑
Urinary cyclic AMP	↑	N/↓	N/↓	N/↓	↑	N	N/↑
Urinary cyclic AMP (fasting)	↑	N	N	N	↑	N	N/↑
α	↑/N	↑	↑/N	↑/N	↑/N	N	↓
Urinary Ca (1-gram Ca load)	↑/N	↑	↑	↑	↑/N	N	↓
Urinary Ca (fasting)	↑/N	N	N	N	↑		↓
Bone density	N/↓	N	N	N	N/↓	N	N/↓
Urinary uric acid	N/↑	N/↑	N/↑	N/↑	N/↑	↑	↓
Urinary oxalate	N/↑	N/↑	N/↑	N/↑	N/↑	N	↑

Fasting samples represent 2-hour urine collections obtained in the morning following an overnight fast. 1-gram Ca load samples were obtained over a 4-hour period subsequent to an oral ingestion of 1 g Ca. Fractional Ca absorption (α) was obtained from fecal recovery of radioactivity following oral administration of radiocalcium with 100 mg Ca. Bone density was obtained in the distal third of the radius by photon absorptiometry. PTH = immunoreactive parathyroid hormone; ↑ = high; ↓ = low; N = normal; PHPT = primary hyperparathyroidism, AH-I = absorptive hypercalciuria Type I; AH-II = absorptive hypercalciuria Type II; AH-III = hypophosphatemic absorptive hypercalciuria; RH = renal hypercalciuria; HUCU = hyperuricosuric calcium oxalate nephrolithiasis (pure presentation); EH = enteric hyperoxaluria.

than 5.5. Hyperuricosuria may be the only abnormality present in patients with calcium stones, or it may coexist with various forms of hypercalciuria.[7]

Hyperoxaluria, defined as urinary oxalate >44 mg/day, is associated with calcium oxalate stones. If urinary oxalate is >80 mg/day, primary or enteric hyperoxaluria[51,52] is probably present. In primary hyperoxaluria, urinary glycolate or glycerate may be increased in addition to oxalate. Moreover, oxalosis (tissue deposition of calcium oxalate), anemia, and renal failure are common in primary hyperoxaluria. In enteric hyperoxaluria, there is a history of small bowel disease, ileal bypass, or resection. Urinary calcium is typically low (<100 mg/day). Serum calcium and magnesium may be low or low normal, and parathyroid function may be stimulated. Serum bicarbonate and urinary citrate may be reduced.[54,55] Even in the absence of intestinal disease, a mild to moderate hyperoxaluria (urinary oxalate 44-80 mg/day) may occur with vitamin C therapy, overindulgence with oxalate-rich foods (particularly spinach), or severe dietary calcium deprivation. Mild hyperoxaluria may also be seen in patients with increased calcium absorption, such as those suffering from absorptive hypercalciuria.

One of the causes of inhibitor deficiency is renal tubular acidosis. Renal tubular acidosis is characterized by systemic hyperchloremic metabolic acidosis and high urinary pH (>6.8) in the absence of infection. Hypokalemia may also be present. Nephrocalcinosis is more common than nephrolithiasis, but calcium stones may occur. There is also an incomplete form of renal tubular acidosis characterized by normal serum pH and bicarbonate but an impaired ability to acidify the urine following ammonium chloride load. Both complete and incomplete forms may be associatd with hypercalciuria and low urinary citrate (<320 mg/day).[54,59] Urinary citrate may also be reduced in some patients with calcium nephrolithiasis independently of a defect in acidification.[54]

Uric acid lithiasis is disclosed by the finding of uric acid on stone analysis. Typically, urinary pH is unusually low (<5.5), and serum uric acid high. Urinary uric acid may be normal or high. A microscopic examination of urinary sediment may show the presence of uric acid crystals.

In cystinuria, the cyanide-nitroprusside test provides a qualitative measure of the cystine content of urine. If positive, a quantitative test should be performed. In patients with cystine stones, urinary cystine is increased (>400 mg/day).

Infection lithiasis is disclosed by the presence of magnesium ammonium phosphate on stone analysis. Such struvite stones are often associated with pyuria, positive urine culture for urea-splitting organisms (Proteus, certain species of Staphylococcus, Pseudomonas, and Klebsiella), and high urinary pH (>7.0). Struvite stones are radioopaque and sometimes may attain a large (staghorn) size. Struvite stones usually occur as mixtures with calcium carbonate apatite, and less commonly with calcium oxalate.

Using this protocol, 11 metabolic causes of nephrolithiasis were identified (Table 7). No physiological derangements were identified in only 5.4% of patients (no metabolic abnormality). However, 5.4% of patients had unclassified hypercalciuria, since the exact physiological basis for the hypercalciuria could not be ascertained. Most of these unclassified patients had fasting hypercalciuria with normal parathyroid function. This presentation has often been erroneously classified as renal hypercalciuria.

Table 7.

Classification of nephrolithiasis

Absorptive hypercalciuria	54.3
Type I	
Type II	
Type III	
Renal hypercalciuria	8.3
Unclassified hypercalciuria	5.4
Primary hyperparathyroidism	5.8
Hyperuricosuric calcium urolithiasis	8.7
Enteric hyperoxaluria	2.1
Uric acid lithiasis	2.1
Infection lithiasis	2.1
Renal tubular acidosis	0.4
Hypocitraturia	5.4
No metabolic abnormality	5.4

Our preliminary data indicate that fasting hypercalciuria with normal parathyroid function may be further characterized from the response to sodium cellulose phosphate therapy. In patients with absorptive hypercalciuria Type I maintained on a diet restricted in calcium (400 mg/day) and sodium (100 meq/day), the inhibition of intestinal calcium absorption by sodium cellulose phosphate (15 g/day) produces an efficient hypocalciuric response, with the decrement in urinary calcium approximating 50% of initial calcium excretion (Fig. 7). Following treatment, fasting urinary calcium and serum PTH are normal. In patients with renal hypercalciuria, the decrement in urinary calcium is sometimes subnormal and fasting hypercalciuria sometimes persists following sodium cellulose phosphate treatment. In some patients with renal hypercalciuria, hypocalciuric response is adequate and normal fasting urinary calcium is restored; however, serum PTH is increased.

Based on the hypocalciuric response to sodium cellulose phosphate treatment we are currently exploring the possibility of simplifying our outpatient diagnostic protocol as follows:

Patients will be instructed to be maintained on a diet limited to 400 mg calcium/day and 100 meq sodium/day for 7 days. During the last 3 days of the diet (Days 5, 6, and 7), they will take sodium cellulose phosphate 5 g tid with meals. (If they take an evening snack, they will divide 5 g dose between breakfast and snack. They will not take any other snack). On day 4 (prior to sodium cellulose phosphate treatment) and on Day 7 (during treatment), they will collect 24-hour urine for calcium, creatinine, Na, K, Mg, citrate, oxalate, phosphorus, uric acid, total volume, and pH. On Day 8, they will obtain a 2-hour fasting urine sample following a 12-hour overnight fast for Ca, creatinine, pH, Na, K, volume, and cyclic AMP. On the morning of Day 8, venous blood will be obtained for SMA-20 and PTH.

"Rational" Therapy of Nephrolithiasis

Improved elucidation of pathophysiology and formulation of diagnostic criteria for different causes of nephrolithiasis have made feasible the

Fig. 7.

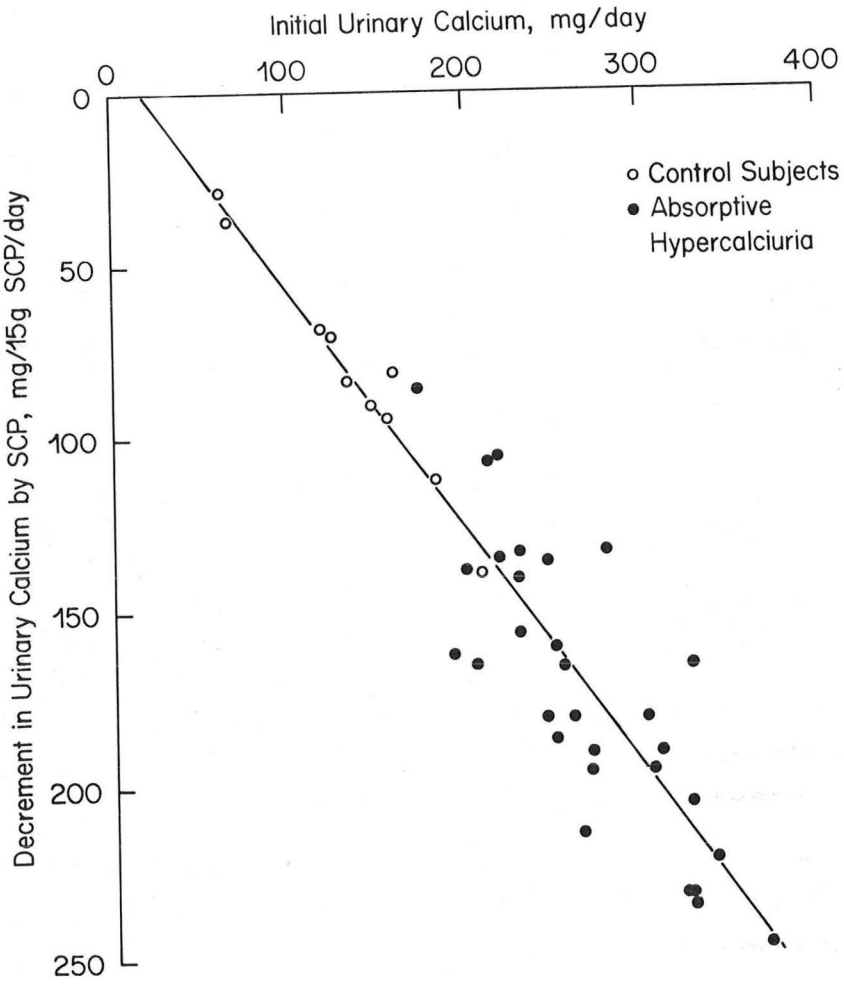


Fig. 7. The decrement in urinary calcium produced by sodium cellulose phosphate therapy (SCP) (15 g/day). The diagonal line represents regression line. The initial urinary calcium was less than 200 mg/day in 3 patients in this study; however, their urinary calcium exceeded 200 mg/day previously.

adoption of selective or optimum treatment program.[8,64] Such programs should (a) reverse the underlying physicochemical and physiological derangements, (b) inhibit new stone formation, (c) overcome non-renal complications of the disease process, and (d) be free of serious side-effects.[64] The rationale for the selection of certain treatment programs is the assumption that the particular physicochemical and physiological aberrations identified with the given disorder are etiologically important in the formation of renal stones (as previously discussed), and that the correction of these disturbances would prevent stone formation. Moreover, it is assumed that such a selective treatment program would be more effective and safe, than a "random" treatment.

For many treatment programs recommended for nephrolithiasis, sufficient information is now available to characterize their physicochemical (Table 8) and physiological actions (Table 9). Based on these actions, it may be possible to suggest optimal indications.

TABLE 8 *Physicochemical effects of therapeutic modalities*

	Parathyroidectomy	Sodium Cellulose Phosphate	Orthophosphate	Diphosphonate	Thiazide	Allopurinol	Magnesium	Water
Urinary calcium	Moderate decrease	Marked decrease	Mild decrease	No change	Moderate decrease	No change	Mild increase	No change
Urinary phosphorus	No change	Mild increase	Marked increase	No change	Mild increase/ no change	No change	Mild decrease	No change
Urinary oxalate	No change/ mild decrease	Mild increase	Mild increase/ no change	Mild increase/ no change	Mild increase/ mild decrease	No change	Mild decrease	No change
Urinary citrate	Mild decrease	No change	Mild increase	No change	Mild decrease	No change	No change	No change
Urinary pyrophosphate	Mild decrease	No change	Moderate increase	No change	Mild increase	Mild increase/ no change	No change	No change
Brushite:								
Activity product ratio or state of saturation	Mild decrease	Moderate decrease	Mild increase	No change	Mild decrease	No change	Mild increase	Moderate decrease
Formation product ratio or limit of metastability	Mild increase	No change	Mild increase	Mild increase	Mild increase	Mild increase/ no change	No change	No change
Crystal growth	Mild decrease	No change	Mild decrease/ no change	Mild decrease	No change	No change	No change	—
Calcium oxalate:								
Activity product ratio or state of saturation	Mild decrease	Mild decrease/ no change	Mild decrease	No change	Mild decrease	No change	No change	Moderate decrease
Formation product ratio or limit of metastability	Mild increase	No change	Mild increase	Mild increase	Mild increase	Mild increase	No change	Mild increase
Crystal growth	Mild decrease	No change	Mild increase/ no change	Mild decrease	No change	Mild decrease	No change	—
Aggregation	—	—	Mild decrease	Mild decrease	—	—	—	—

TABLE 9 *Physiological actions of therapeutic modalities*

	Primary Action	Secondary Action
Parathyroidectomy	Decrease PTH	Decrease serum calcium, calcium absorption, urinary calcium
Sodium cellulose phosphate	Decrease intestinal calcium absorption	Decrease urinary calcium
Orthophosphate	—	Decrease urinary calcium, increase citrate and pyrophosphate
Diphosphonate	Increase urinary diphosphonate	
Thiazide	Decrease urinary calcium	Decrease calcium absorption in renal hypercalciuria, not in absorptive hypercalciuria
Allopurinol	Decrease uric acid synthesis	Decrease urinary uric acid
Magnesium	Increase urinary magnesium, decrease oxalate absorption	
Water	Increase urine output	Decrease urinary concentration of stone-forming substances

This selective approach differs from the more randomized treatment program in which the same drug may be used for several causes, even though its actions may be poorly defined. We shall review available data concerning the ability of selective treatments to restore normal urinary environment and inhibit new stone formation, for some of the major causes of nephrolithiasis where we have personal experience.

Mode of action and efficacy of selective treatments

Sodium cellulose phosphate for absorptive hypercalciuria Type I.

There is currently no treatment program which is capable of correcting the basic abnormality of absorptive hypercalciuria Type I, although several drugs are available which have been shown to restore normal calcium excretion. Sodium cellulose phosphate best meets the criteria for optimum therapy.[5,65] When given orally, this nonabsorbable exchange resin binds calcium and inhibits calcium absorption. However, this inhibition is caused by limiting the amount of intraluminal calcium available for absorption, and not by correcting the basic disturbance in calcium transport.

The above mode of action accounts for the three potential complications of sodium cellulose phosphate therapy. First, it may cause negative calcium balance and parathyroid stimulation if it is used in patients with normal intestinal calcium absorption or with renal or resorptive hypercalciuria. Second, the treatment may cause magnesium depletion by binding magnesium as well.[65] Third, sodium cellulose phosphate may produce secondary hyperoxaluria, by binding divalent cations in the intestinal tract, reducing divalent cation-oxalate complexation, and making more oxalate available for absorption.[65] These complications may be overcome by using the drug only in documented cases of absorptive hypercalciuria Type I, applying oral magnesium supplementation (1.0-1.5 magnesium gluconate twice/day, separately from sodium cellulose phosphate), and by imposing a moderate dietary restriction of oxalate. A dietary table useful in an outpatient management of this condition is given in Table 10.

When above precautions are followed, sodium cellulose phosphate at a dosage of 10-15 g/day (given with meals) has been shown to reduce urinary calcium and saturation of calcium salts (calcium phosphate as well as calcium oxalate),[15] maintain stable bone density (Fig. 8), and to be clinically effective in studies at Dallas.[8] This treatment reduced the stone formation rate from 2.28 stones/patient year to 0.23/patient year ($p<0.001$ by chi square test), caused remission in 77.8% of patients and lowered individual stone formation rate in all patients (Fig. 9).

Table 10.

LIMITED (IN CALCIUM, SODIUM, OXALATE) DIET

This diet limits calcium and sodium. Certain foods that have large amounts of oxalate are also limited.

	FOODS ALLOWED	FOODS NOT ALLOWED
BEVERAGES	Carbonated drinks; coffee; lemonade, limeade; decaffeinated coffee; instant tea	ALL MILK including canned milk, eggnog, milkshakes, malted milk, powdered milk and buttermilk; hot chocolate, cocoa mixes; brewed tea
BREAD & CEREALS	Biscuits, bread, buns (hamburger), cornbread, muffins, pancakes, sweet rolls, flour tortillas, waffles; cooked and dry cereals.	Salt topped bread, crackers and rolls; corn tortillas.
CHEESE	NONE	ALL CHEESE including cheddar cheese, cheese crackers, cheese foods, cheese puffs, cheese sauces, cheese sticks, cheese spreads, cottage cheese, cream cheese, dips, gouda, Parmesan cheese, processed cheese, provaloni, romano and Swiss cheese.
DESSERTS & SWEETS	Honey, jelly, jam, marmalade, preserves, syrup, sugar; fruit cobblers and fruit pies; gelatin desserts; white and yellow cake with sugar icing, shortcake; bread pudding (no milk), tapioca; lemon sauce made with cornstarch; cookies, vanilla wafers, graham crackers; fruit ices and popsicles.	Molasses; chiffon pie and cream pie; ALL CHOCOLATE in cakes, icings, pies and cookies, chocolate chips and chocolate syrup; pudding, custard; Boston cream pie; rice pudding; yogurt; ALL ICE CREAM, mellorine, frozen custard, ice milk, sherbet and "dietetic" ice cream.
FATS	Butter, margarine, vegetable oil, and most salad dressings; powdered or liquid non-dairy creamer; non-dairy whipped topping.	Salad dressings made with cheese or sour cream; cream, 1/2 & 1/2 cream.
FRUITS & JUICES	Fresh, canned and frozen fruit; fresh, canned and frozen fruit juice.	Dried fruits; tomato juice and vegetable juice cocktail; powdered fruit juice substitutes, Rhubarb.
MEATS & MEAT SUBSTITUTES	Eggs. TWO AVERAGE PORTIONS PER DAY of baked, boiled, broiled or fried beef, chicken, fresh water fish, fresh pork, seafood, tuna, turkey, veal or venison; homemade chili, meat pies and stews.	Barbequed, cured, salty or smoked meat and fish; bacon, anchovies, canned meat and stews, canned salmon, caviar, canned chili, corned beef, corned beef hash, dried chipped beef; frankfurters, ham, herring; luncheon meats; frozen meat pies, pizza, salt pork, sardines, tamales, sausage, T.V. dinners. (Unless low sodium content indicated).

	FOODS ALLOWED	FOODS NOT ALLOWED
STARCHES	Corn, macaroni, noodles, potatoes, rice, and spaghetti; dried beans and dried peas in moderation.	Macaroni and cheese; potato chips, corn chips, tortilla chips; corn pudding.
VEGETABLES & SOUPS	Fresh, canned and frozen vegetables; homemade soups.	Sauerkraut and other vegetables prepared in brine; canned pork & beans hominy; ALL "GREENS" such as turnip greens, spinach, collard greens, mustard greens, beet greens and polk; cheese soups, canned broth, bouillon cubes, canned soup (unless low sodium content indicated).
MISCELLANEOUS	Spices, herbs and extracts; unsalted peanut butter, SMALL AMOUNTS of meat tenderizer, brown gravy and sauces such as catsup, chili sause, spaghetti sauce, steak sauce and worcestershire sauce because these DO CONTAIN SALT!	ADDED SALT, seasoned salt, monosodium glutamate (MSG), prepared horseradish and mustard; olives, pickles, salted nuts, salted popcorn; regular peanut butter; soysauce; cream gravies and white sauce, hollandaise, newburg sauce.
SUPPLEMENTS	NONE	Vitamins plus minerals, and VITAMIN C.
MEDICATIONS	As directed by physician.	

INSTRUCTIONS FOR LIMITING SALT:

1. Use no salt or seasoned salt at the table.

2. Eat foods only lightly salted during preparation.

3. Do not add salt in the preparation of foods to which salt is added in processing. Example: canned vegetables.

4. When preparing food from a recipe, use half the amount of salt specified.

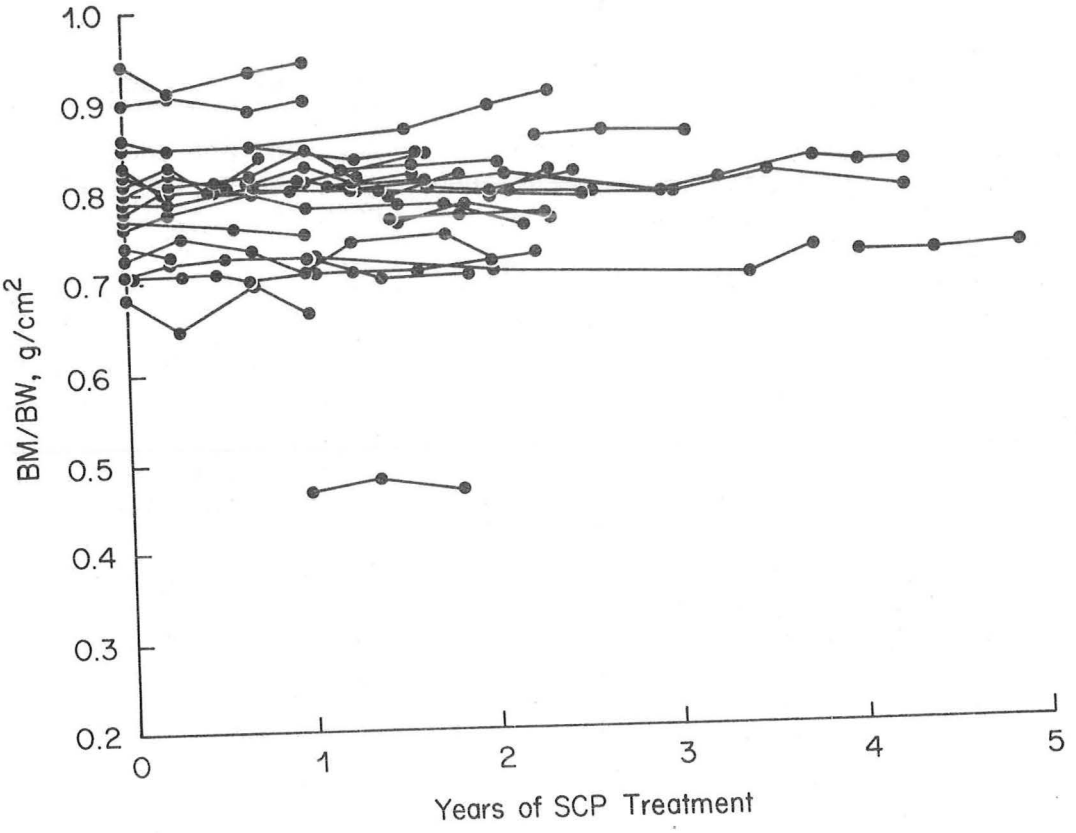


Figure 8. Effect of sodium cellulose phosphate (SCP) therapy on bone density (BM/BW). Points connected by solid line represent study in same patient.

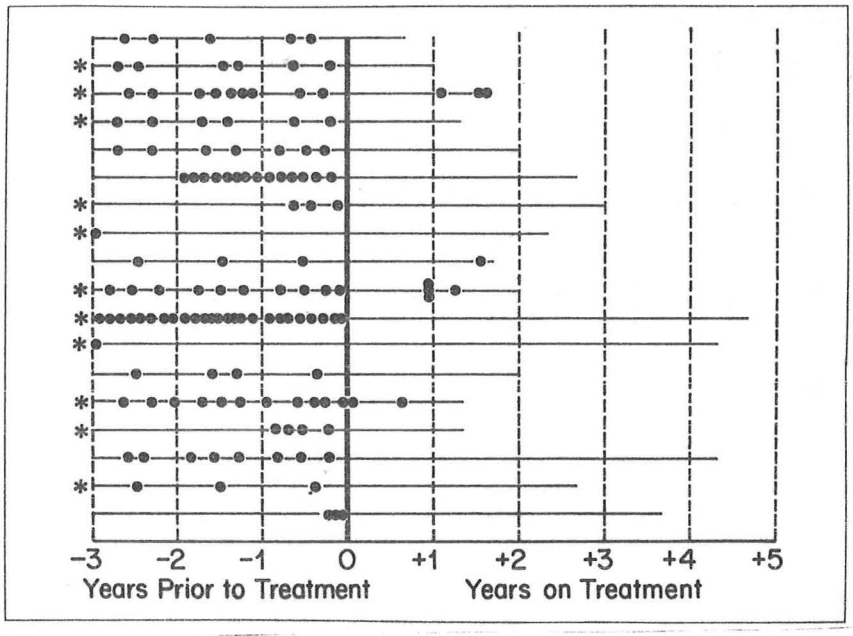


Figure 9. *Effect of sodium cellulose phosphate on new stone formation in absorptive hypercalciuria Type I. Each line represents study in a separate patient. Asterisk before each line indicates presence of preexisting renal stone(s). Each point shows new stone formation.*

Conservative treatment of absorptive hypercalciuria Type II. The features of absorptive hypercalciuria Type II are identical to those of absorptive hypercalciuria Type I, except for normocalciuria (<200 mg/day) on a diet of 400 mg calcium and 100 meq sodium/day.[7] In addition, many

patients show disdain for drinking fluids and excrete concentrated urine.[7] A low calcium intake (400-600 mg/day) and high fluid intake (sufficient to achieve a minimum urine output of 2 liter/day) would seem ideally indicated,[8] since normocalciuria could be restored by dietary calcium restriction alone, and increased urine volume has been shown to reduce urinary saturation of calcium oxalate, brushite and monosodium urate, and inhibit spontaneous nucleation of calcium oxalate.[66]

In 24 patients so treated, stone formation rate decreased from 1.83 stones/patient year to 0.38/patient year ($p<0.001$), 70.8% of patients were in remission over a mean follow-up of 2.32 years/patient, and individual stone formation declined in 22 patients (91.7%) (Fig. 10).

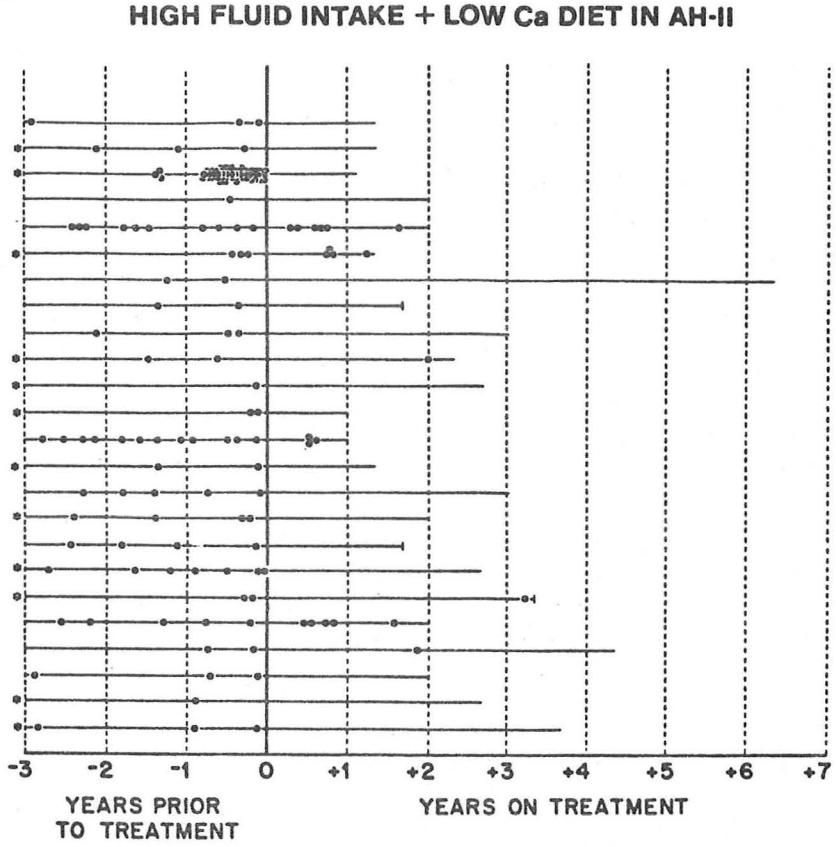


Figure 10. Effect of high fluid intake and low calcium diet on renal stone formation in absorptive hypercalciuria Type II (AH-II). Each line represents study in a separate patient. Each circle represents a new stone episode (formation or passage). Asterisk indicate preexisting stones when treatment was begun. Vertical line at zero represents time when treatment was initiated.

Orthophosphate for absorptive hypercalciuria Type III. Orthophosphate (neutral or alkaline salt of sodium and/or potassium, 0.5 g phosphorus 3-4 times/day) would seem to be the logical treatment because of its potential for the inhibition of $1,25\text{-}(OH)_2D$ synthesis.[44] However, there is as yet no convincing evidence that this treatment restores normal intestinal calcium absorption in this condition.[44] Orthophosphate reduces urinary

calcium probably by directly impairing the renal tubular reabsorption of calcium. Urinary phosphorus is markedly increased during therapy, a finding reflecting the absorbability of soluble phosphate.[15] Physicochemically, orthophosphate reduces urinary saturation of calcium oxalate[67] but increases that of brushite.[15] Moreover, the urinary inhibitor activity is increased, probably owing to the stimulated renal excretion of pyrophosphate and citrate. Although contrary reports have appeared, this treatment program has been reported to cause soft tissue calcification[68] and parathyroid stimulation. It is contraindicated in nephrolithiasis complicated by urinary tract infection.

In our experience, orthophosphate treatment lowered stone formation from 2.38 stones/patient year to 0.36/patient year ($p<0.001$), produced a remission in 62.5% of patients over a mean follow-up of 4.13 years/patient, and caused a reduced stone formation rate individually in all patients.[8]

Thiazide for renal hypercalciuria. Thiazide is ideally indicated for the treatment of renal hypercalciuria. This diuretic has been shown to correct the renal leak of calcium, by augmenting calcium reabsorption in the distal tubule, and by causing extracellular volume depletion and stimulating proximal tubular reabsorption of calcium. The ensuing correction of secondary hyperparathyroidism[69] restores normal serum $1,25\text{-}(OH)_2D$ and intestinal calcium absorption.[29] Physicochemically, the urinary environment becomes less saturated with respect to calcium oxalate and brushite during thiazide treatment, largely because of the reduced calcium excretion.[15,70] Moreover, urinary inhibitor activity, as reflected in the limit of metastability, is increased by an unknown mechanism.[15] These effects are shared by hydrochlorothiazide 50 mg twice/day, chlorthalidone 50 mg/day or trichlormethiazide 4 mg/day. Potassium supplementation (40-60 meq/day) may sometimes be required to prevent hypokalemia and attendant hypocitraturia.[61,71] Concurrent use of triamterene, a potassium-sparing agent, should be undertaken with caution because of recent reports of triamterene stone formation.[72] However, amiloride may be used with thiazide, since it alone has sometimes been shown to exert a hypocalciuric action, exaggerate the hypocalciuric action of thiazide and to prevent hypokalemia.[73] Thiazide is contraindicated in primary hyperparathyroidism, because of potential aggravation of hypercalcemia.[74]

During this treatment, stone formation decreased from 1.83 stones/patient year to 0.40/patient year ($p<0.001$), and remission was encountered in 75% of patients.[8]

Allopurinol for hyperuricosuric calcium oxalate nephrolithiasis. Allopurinol (100 mg three times/day) is the physiologically meaningful drug of choice in hyperuricosuric calcium oxalate nephrolithiasis resulting from uric acid overproduction, because of its ability to reduce uric acid synthesis and lower urinary uric acid. Its use in hyperuricosuria associated with dietary purine overindulgence is also reasonable, since dietary purine restriction is impractical. Physicochemical changes ensuing from restoration of normal urinary uric acid include an increase in the urinary limit of metastability of calcium oxalate.[18] Thus, the spontaneous nucleation of calcium oxalate is retarded by treatment, probably via inhibition of monosodium urate-induced stimulation of calcium oxalate crystallization.[19]

Because of the potential exaggeration of monosodium urate-induced calcium oxalate crystallization,[19] a moderate sodium restriction (<150 meq/day) is also advisable.

In our study involving a mean allopurinol treatment period of 2.28 years/patient, stone formation rate decreased from 1.00 stone/patient year to 0.09/patient year ($p<0.001$), 83.3% of patients were in remission, and individual stone formation was reduced in 95.8% of patients (Fig. 11).

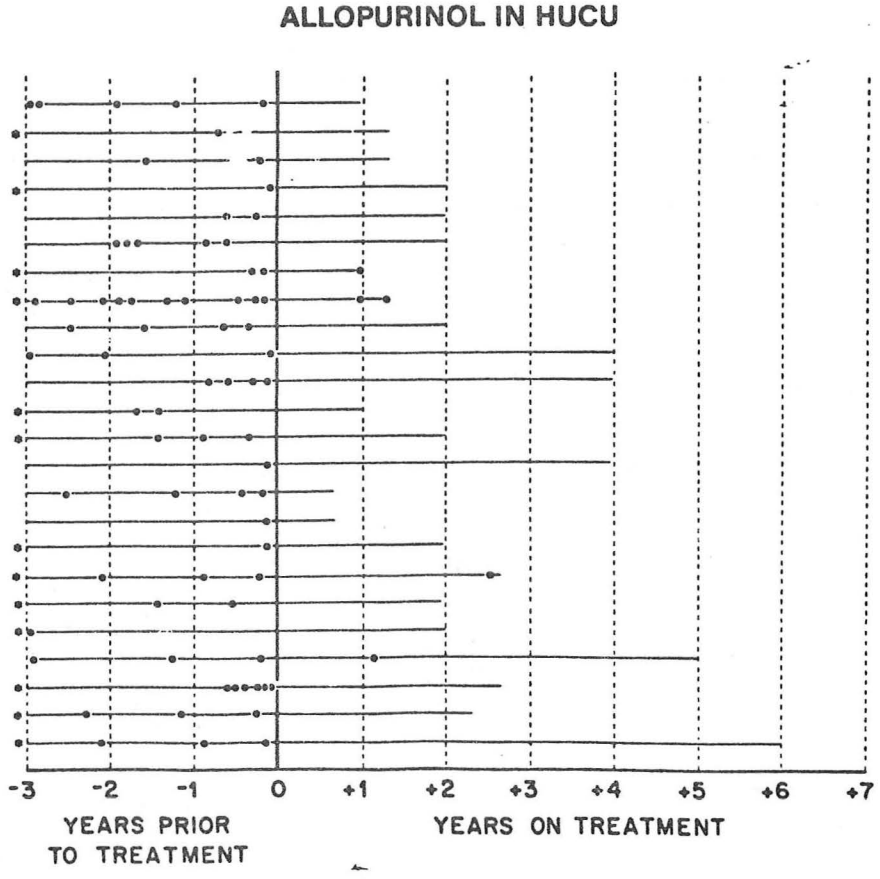


Figure 11. Effect of allopurinol treatment on stone formation.

Potassium citrate for uric acid lithiasis and hypocitraturic calcium nephrolithiasis. In patients with uric acid lithiasis, potassium citrate (approximately 20 meq three times/day) effectively raises urinary pH to normal levels at which uric acid is more soluble. In patients with hypocitraturic calcium nephrolithiasis, potassium citrate treatment is capable of restoring normal urinary citrate, lowering urinary saturation and inhibiting crystallization of calcium salts.[75]

On our General Clinical Research Center with the support of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, we have completed most of the basic and clinical studies required for the approval of new drug application for potassium citrate by the FDA. Four groups of patients were evaluated. Group I comprised 16 patients with renal tubular acidosis or chronic diarrheal syndrome with severe hypocitraturia. Group II was composed of 38 patients with absorptive hypercalciuria or renal hypercalciuria with concurrent hypocitraturia, hypocitraturia as the sole abnormality, or uric acid lithiasis. They received potassium citrate therapy alone since their other abnormalities were not considered severe enough to require specific treatment. Group III was represented by 16 patients (with hyperuricosuric calcium oxalate nephrolithiasis, absorptive hypercalciuria or no metabolic abnormality) who

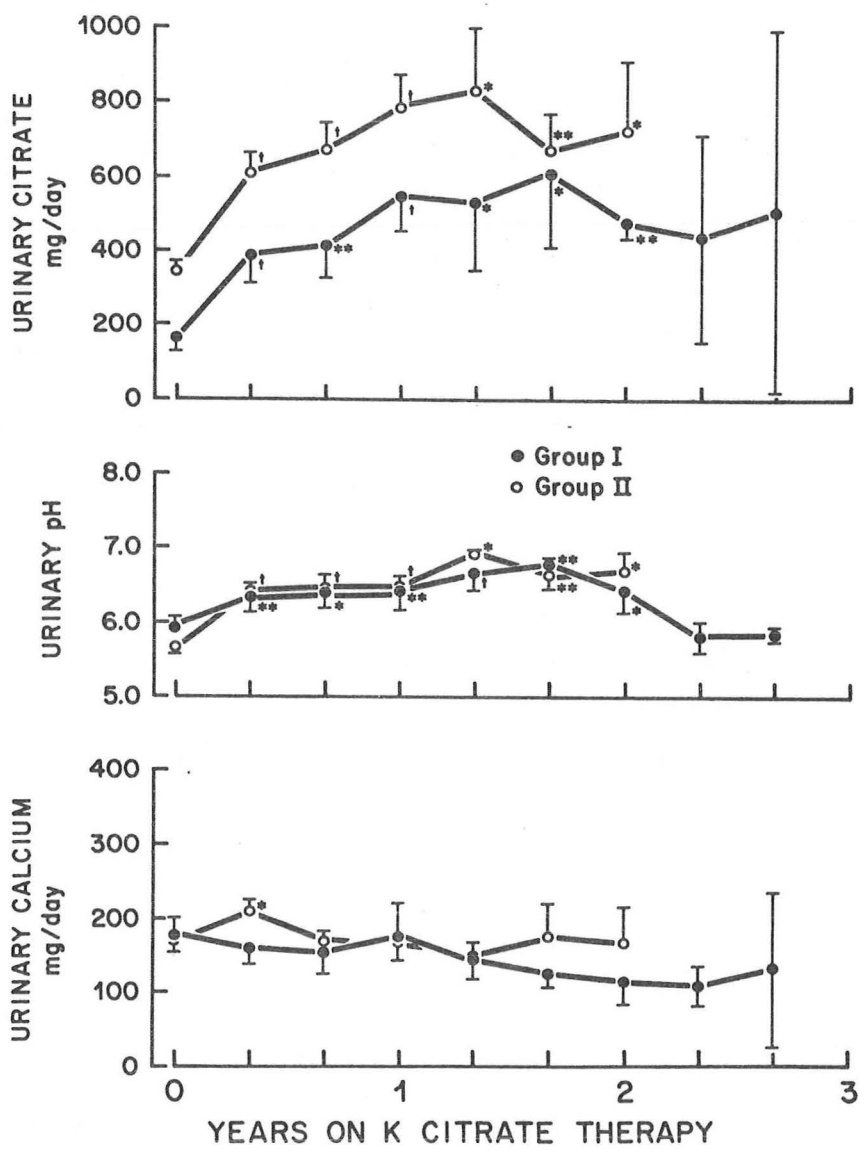


Fig. 12. Effect of long-term potassium citrate on urinary citrate, pH and calcium in Groups I and II. Bars indicate mean ± SE. Significant difference from the pre-treatment value, determined by paired t-test, is shown by * for $p<0.05$, ** for $p<0.01$ and + for $p<0.001$.

relapsed (or continued to form stones) on allopurinol, thiazide or conservative therapy. Because they were later found to have hypocitraturia, potassium citrate was added to the ongoing treatment program. Group IV consisted of 14 patients who presented with hypocitraturia as well as other abnormalities (hypercalciuria, hyperuricosuria). They received potassium citrate with thiazide and/or allopurinol.

During treatment, urinary citrate which was below normal to begin with increased to the normal range (Fig. 12, Fig. 13). Urinary pH significantly increased, but remained below 7. There was no significant change in urinary calcium during treatment with potassium citrate in this outpatient study, although this treatment was shown to significantly reduce urinary calcium in patients with uric acid lithiasis during an inpatient study.[76]

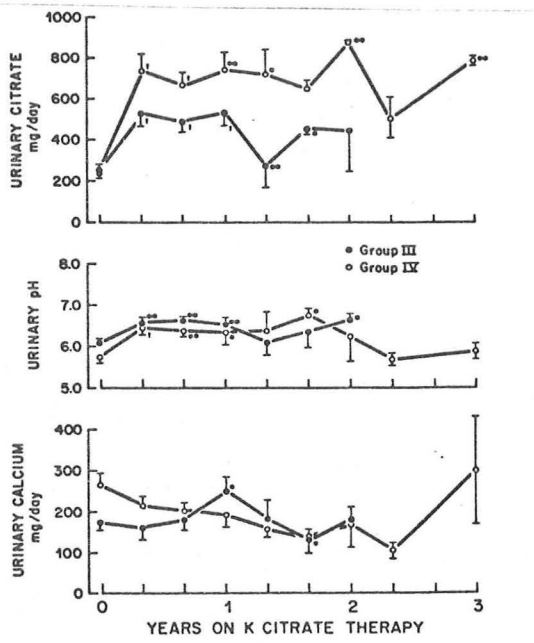


Figure 13. Effect of long-term potassium citrate on urinary citrate, pH and calcium in Groups III and IV.

The relative saturation ratio of calcium oxalate in urine declined during treatment with potassium citrate (Fig. 14).[75] Thus, the urinary environment, which was supersaturated with respect to calcium oxalate to begin with, became less saturated following treatment, probably because of citrate complexation of calcium and the resulting reduction in calcium ionic activity. However, the relative saturation ratio of brushite did not change significantly during treatment. The urinary environment remained supersaturated with respect to brushite at approximately the same level, because the effect of increased dissociation of phosphate from the rise in pH was offset by citrate complexation of calcium. Moreover, the treatment significantly increased the permissible increment in oxalate.[75] Thus, more oxalate was required to elicit spontaneous nucleation of calcium oxalate following treatment than before treatment. In an inpatient study, a short-term treatment with potassium citrate was shown to inhibit the spontaneous nucleation of calcium oxalate in urine as reflected by the formation product ratio.[76]

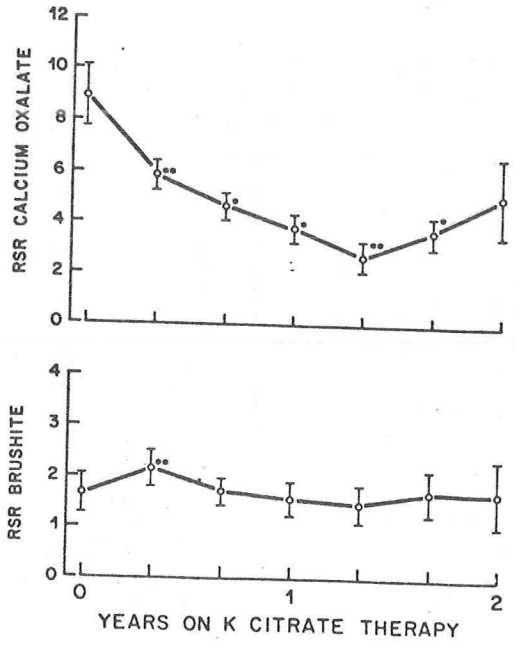


Figure 14. Effect of long-term potassium citrate therapy on the RSR of calcium oxalate and brushite in Group II. Significant differences from the pre-treatment value, determined by paired t-test, is shown by * for $p<0.05$ and ** for $p<0.01$.

In all four groups, potassium citrate therapy inhibited new stone formation (Fig. 15-18). During mean treatment period of 1.08-1.42 years, 77.4% of patients were in remission, and 95.2% patients had reduced stone formation rate individually. The average stone formation rate declined from 4.41±15.38 SD stones/patient year to 0.76±2.05 stones/patient year ($p<0.001$ by chi-square test), upon institution of potassium citrate therapy.

The combined data from all patients showed no significant change in serum potassium, hematocrit, bone density or endogenous creatinine clearance during treatment. Although the liquid preparation of potassium citrate was associated with gastrointestinal complaints in a substantial number of patients, the slow release tablet preparation was well tolerated.

We are currently exploring the possibility that this treatment could cause dissolution of calcium stones in some patients.[75] Approximately 40% of patients have shown a reduced stone mass not entirely accountable by stone passage after treatment with potassium citrate of more than 6 months.

Alphamercaptopropionylglycine (Thiola) for cystinuria. The object of treatment is to reduce the urinary concentration of cystine to below its solubility limit (200-300 mg/day).[12] The initial treatment program includes a high fluid intake to promote an adequate urine flow and oral administration of soluble alkali (e.g. potassium citrate) at a dose sufficient to raise urinary pH to 6.5-7. When this conservative program is ineffective, d-penicillamine (2 g/day in divided doses) has been used. This treatment has been shown to increase cystine solubility in urine via formation of more soluble mixed disulfide. Unfortunately, penicillamine treatment produces frequent side effects, including nephrotic syndrome, dermatitis, and pancytopenia.

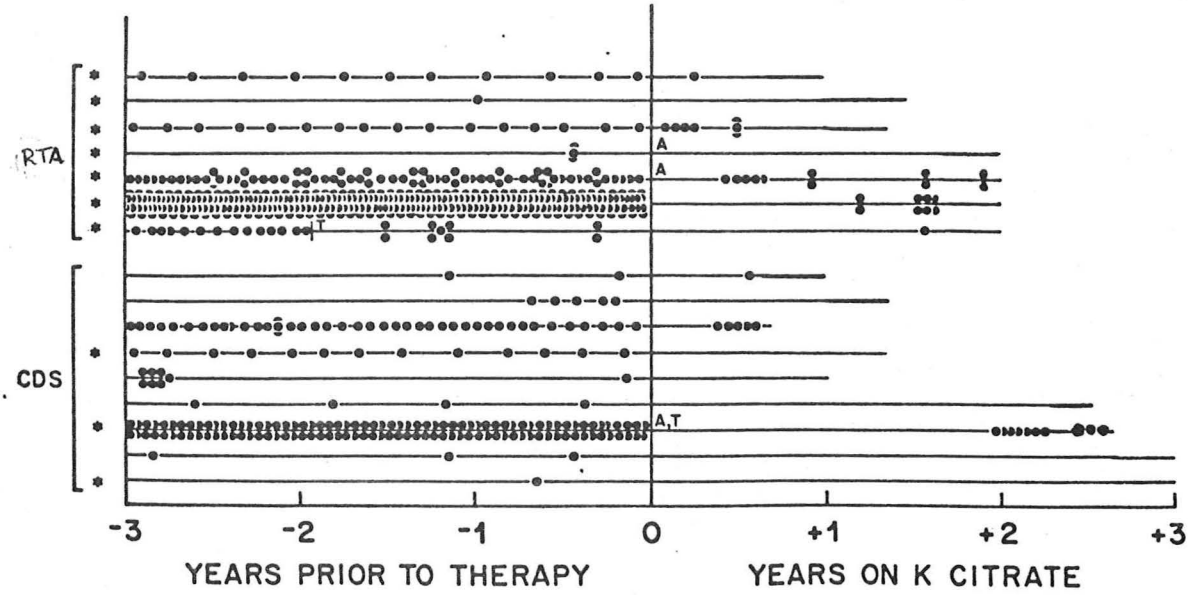


Fig. 15. Updated clinical response to potassium citrate treatment in Group I.

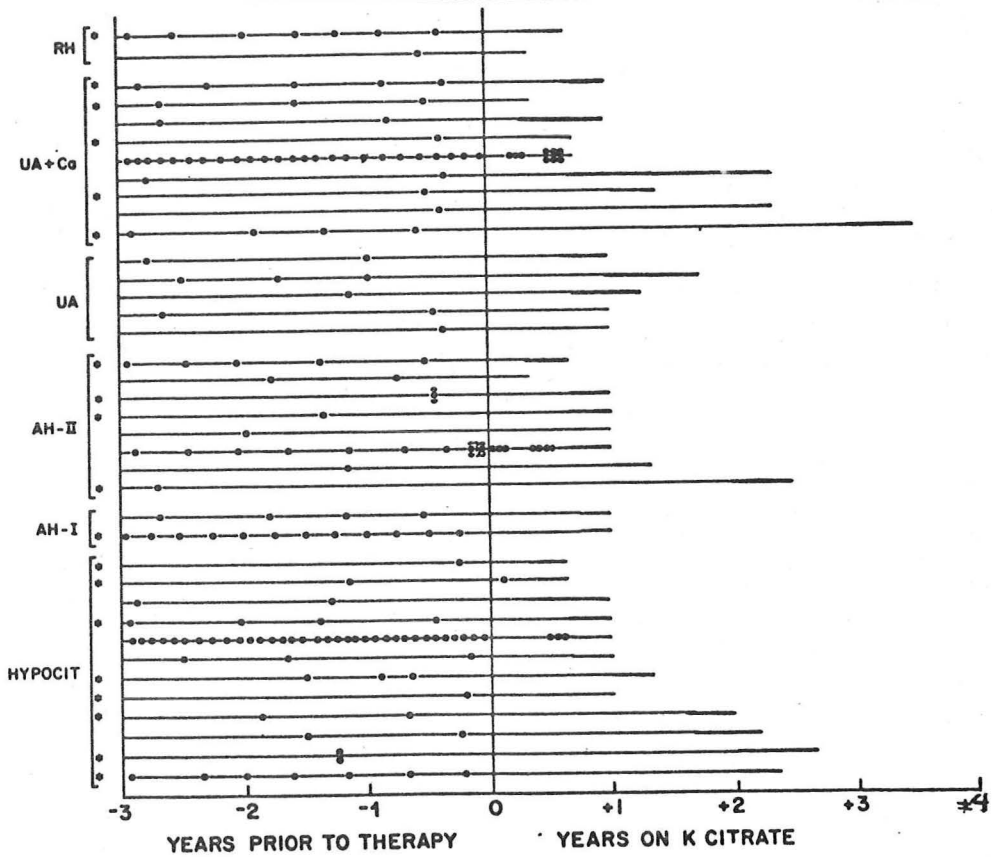


Fig. 16. Updated clinical response to treatment in Group II.

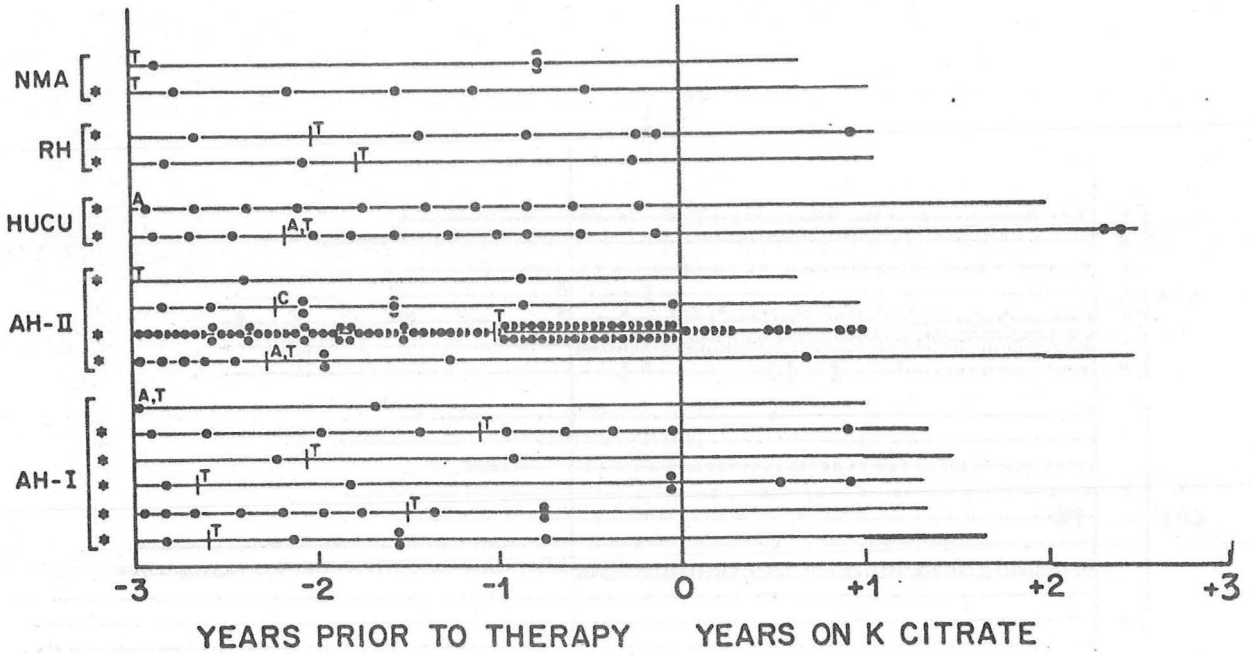


Fig. 17. Updated clinical response to potassium citrate treatment in Group III.

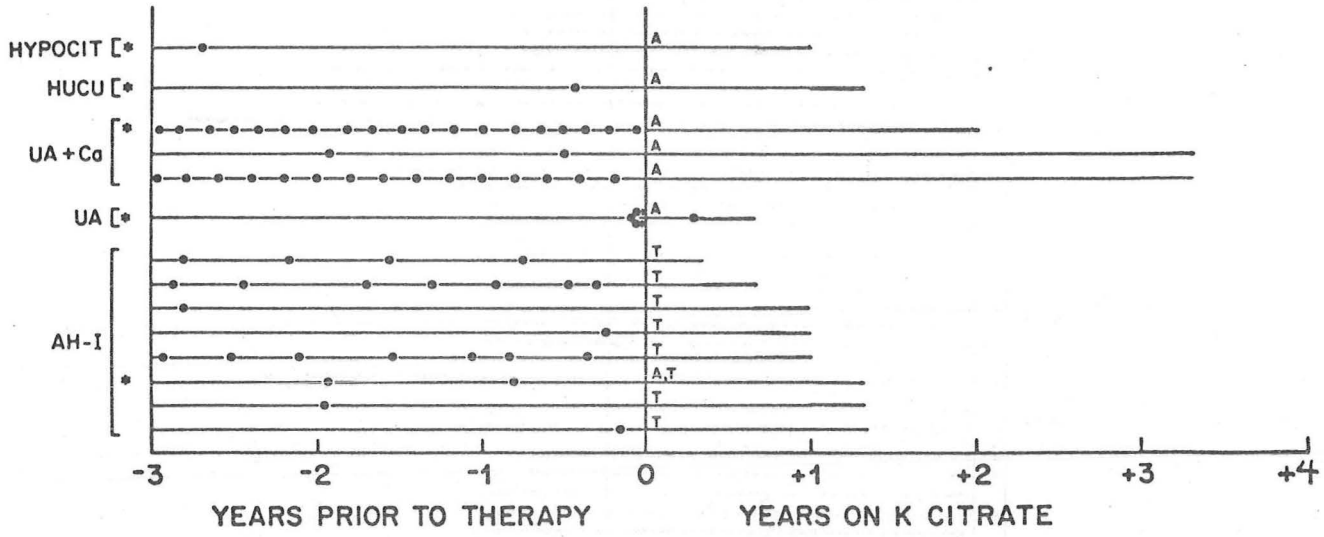


Fig. 18. Updated clinical response to potassium citrate treatment in Group IV.

Studies from abroad indicate that alphamercaptopropionylglycine also forms a mixed disulfide with cysteine, increases solubility of cystine and inhibits stone formation without conferring serious toxicity.[77] We were persuaded by the FDA to organize a multi-clinic trial to test the effectiveness and safety of Thiola. The primary test subjects were cystinuric patients with known toxicity to d-penicillamine. Although approximately 50% of patients also developed side-effects to Thiola, the complications were usually less severe and the remaining half of patients showed no cross-reactivity of toxicity. Moreover, Thiola was shown to significantly reduce the stone formation rate (Fig. 19).

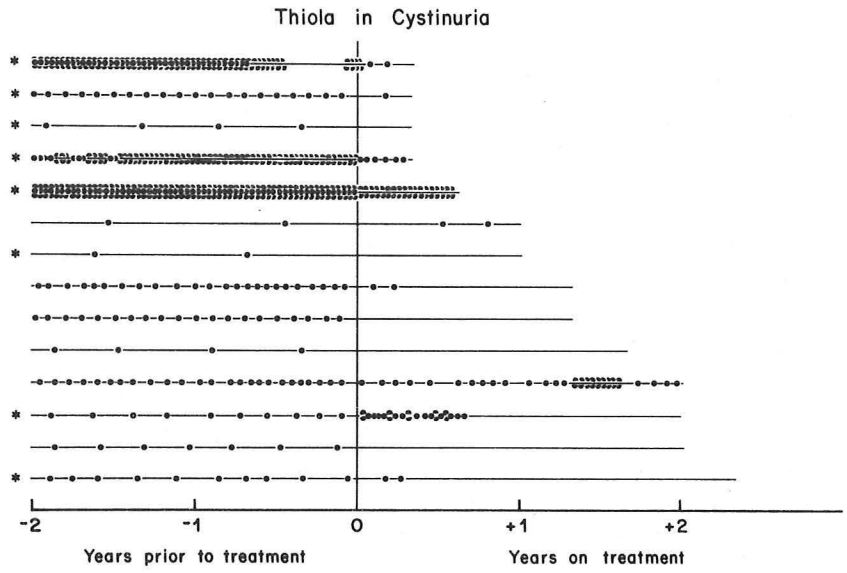


Fig. 19. Effect of Thiola treatment on cystine stone formation.

Conservative treatment for no metabolic abnormality. No metabolic abnormality constitutes the entity in which no clear-cut physiological derangement has been found. However, urine volume is often low, a finding suggesting that a disdain for drinking fluids may have contributed to stone formation. A high fluid intake would appear logical for the same reasons stipulated above.[66]

This conservative treatment program lowered stone formation rate from 1.33 stones/patient year to 0.18/patient year ($p<0.001$), produced remission in 75% and reduced individual stone formation rate in 87.5% of patients (Fig. 20).

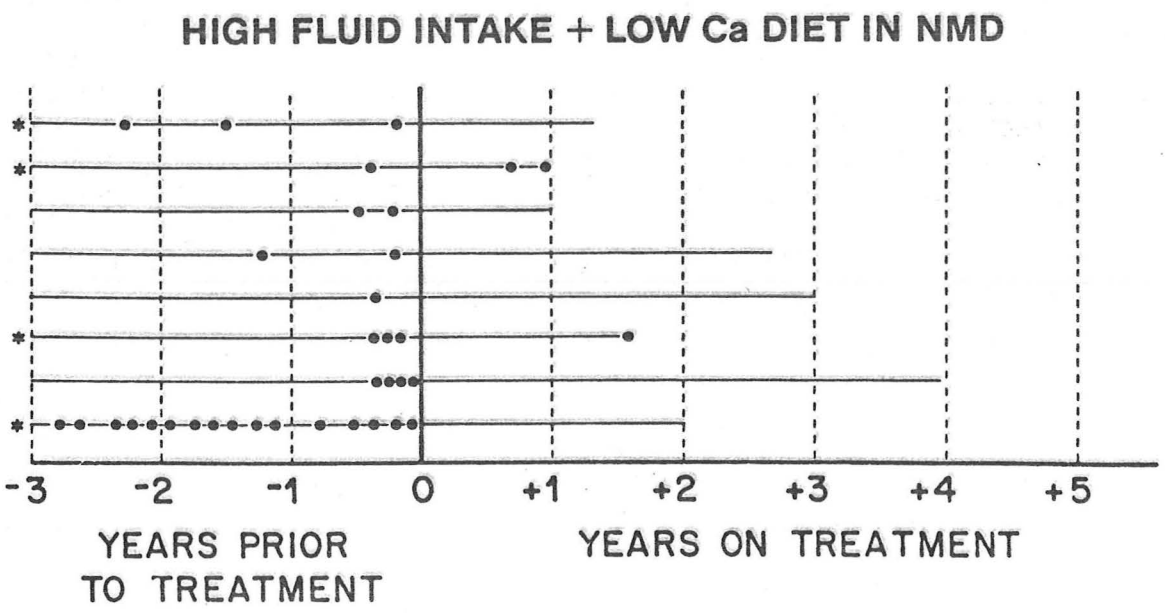


Figure 20. Effect of high fluid intake and low calcium diet on stone formation in no metabolic abnormality (NMA).

Response to less selective treatment programs

Thiazide for absorptive hypercalciuria Type I. Thiazide exerts the same hypocalciuric action and physicochemical effects in absorptive hypercalciuria as in renal hypercalciuria (see treatment of renal hypercalciuria). Unfortunately, the intestinal hyperabsorption of calcium is not corrected by this treatment in absorptive hypercalciuria, unlike in renal hypercalciuria.[28,29] The fate of retained calcium in absorptive hypercalciuria, reflected by the reduced calcium excretion in the face of high calcium absorption, is not known. There is some evidence that the retained calcium is accreted in bone,[21] since bone density has been shown to increase.

With continued treatment, however, the rise in bone density stabilizes, and the hypocalciuric effect of thiazide becomes attenuated. The results suggest that thiazide treatment had caused a low turnover state of bone, which interferes with a continued calcium accretion in the skeleton. The "rejected" calcium would then be excreted in urine (Fig. 21).

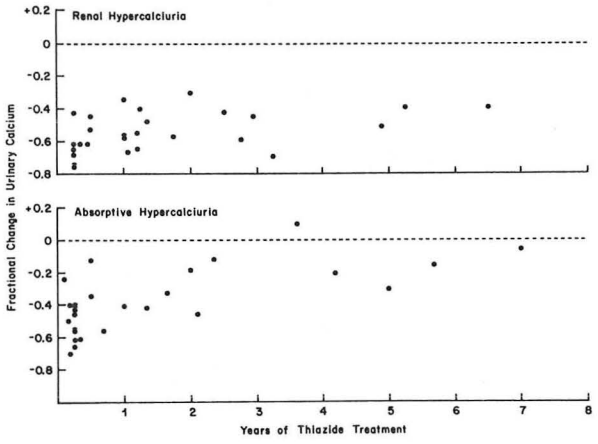


Fig. 21. Decrement in urinary calcium during thiazide therapy.

Moreover, thiazide causes hypokalemia especially if sodium intake is generous and potassium supplement is not provided. The resulting hypokalemia may produce hypocitraturia (Fig. 22).[61] The advantage of potassium citrate over potassium chloride is evident, since it not only prevents the development of hypokalemia but also raises urinary citrate above the control range.[61]

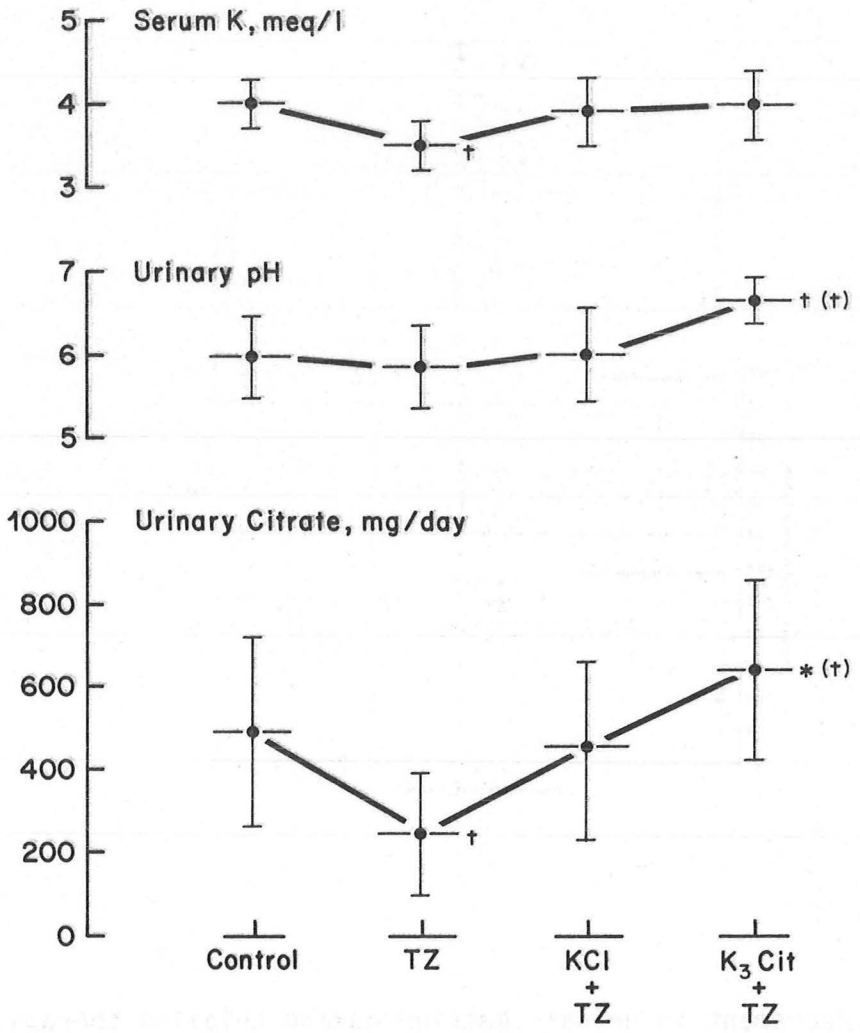
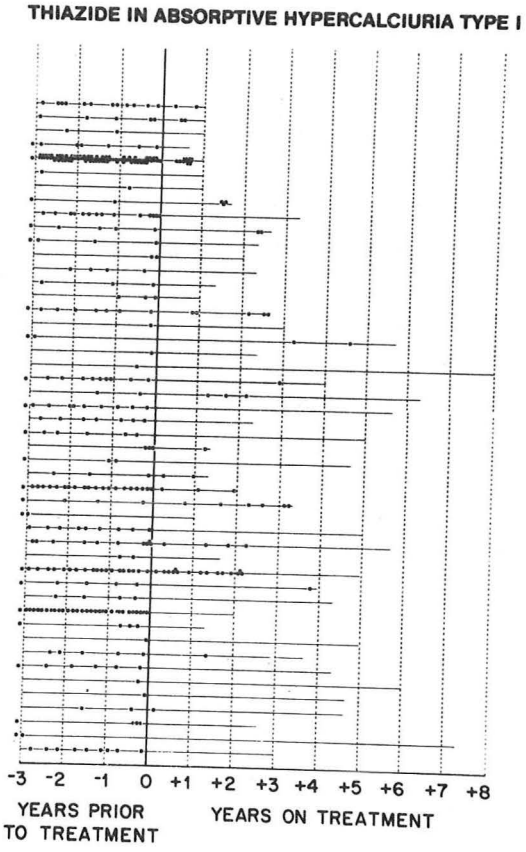


Figure 22. Serum potassium, urinary pH and citrate during the four phases. The four phases included the pretreatment phase (control), thiazide treatment (TZ), thiazide with potassium chloride supplementation (KCL + TZ) and thiazide with potassium citrate supplementation (KCit + TZ). Horizontal bars indicate mean ± SD. Significant difference from values in the control phase is shown by: *$p<0.05$ and +$p<0.001$. Significant difference from values in KCl + TZ vs. KCit + TZ phase is shown by same symbols in parenthesis.

In our experience, thiazide has had limited effectiveness in the prevention of new stone formation in patients with absorptive hypercalciuria Type I (Fig. 23),[14] probably because of the attenuation of hypocalciuric action with continued treatment and the development of hypocitraturia.

Figure 23.



Critique of Clinical Trial

The favorable clinical response to selective treatment programs described above supports, but does not prove, the validity of the concept of a selective treatment approach.[8,64] Since randomized placebo control groups were not included and as pre-treatment history was obtained retrospectively without benefit of direct care, non-specific influences associated with our close follow-up observation could have modified the clinical response to treatment. These non-specific effects probably include change in dietary habits and fluid intake, and improve patient compliance (from close follow-up). Positive "placebo effect" on the course of nephrolithiasis is well known.

Although the need for the assessment of the placebo effect is clear, randomized trials with the inclusion of the placebo control are difficult to conduct because of the difficulty in disguising test medications. Most patients could tell that they are taking sodium cellulose phosphate, thiazide or neutral phosphate.

Validity of the efficacy of selective treatment approach

Despite the lack of randomized control studies, several lines of evidence indicate that selective treatments themselves had exerted a positive impact on the clinical course of stone disease. First, the clinical improvement (reduced stone formation rate) produced by treatment was correlated with objective measures for the propensity of stone formation (reduced saturation of calcium salts in urine).[5] Our preliminary study suggests that the decline in urinary saturation of calcium salts occurring during treatment with sodium cellulose phosphate of patients with absorptive hypercalciuria Type I resulted largely from the effect of treatment itself (reduction in urinary calcium) rather than from non-specific influences (change in urine volume). Second, when patients with absorptive hypercalciuria who had been on sodium cellulose phosphate were placed on alternate treatments, 57.1% of them had a relapse of stone formation (compared to 22.2% during sodium cellulose phosphate treatment).[78] Third, 16 patients who relapsed (continued to form stones on thiazide, sodium cellulose phosphate, allopurinol or conservative therapy) under our care were found to have hypocitraturia. The addition of potassium citrate prevented new stone formation in all but three patients (Fig. 17).[75]

Fourth, a cogent argument may be made for a strong cause and effect relationship between various biochemical disturbances in urine and renal stone formation. All selective treatments chosen were effective in restoring normal urinary composition and in correcting much of the physicochemical disturbances in urine.[15]

Fifth, upon withdrawal of potassium citrate therapy, new stone formation rate which had significantly declined from 3.37±4.47 SD/patient year to 0.45±1.42/patient year ($p<0.05$) rose to the pretreatment range of 11.87±18.10/patient year ($0<0.05$).

Sixth, a recent completed randomized trial in well-diagnosed cases of hyperuricosuric calcium oxalate nephrolithiasis indicated a clear superiority of allopurinol treatment over the placebo in inhibiting new stone formation (Ettinger, B., personal communication).

Other advantages of selective treatment approach

The theoretical advantage of the selective approach is the assumption so far unproved that treatments specifically chosen for their physicochemical and physiological effects are less likely to cause side effects and more likely to overcome extrarenal manifestations of the disease process than a more randomly chosen program.

Hazards of therapy. Although concrete data are lacking it is expected that certain randomized treatments may be associated with significant hazards. Parathyroidectomy in renal hypercalciuria may cause recurrence of renal hypercalciuria and nephrolithiasis.[79] Treatment of renal hypercalciuria with sodium cellulose phosphate may exaggerate secondary hyperparathyroidism and aggravate or produce bone disease.[27] Orthophosphate therapy of normophosphatemic absorptive hypercalciuria may cause calcium retention, since high intestinal calcium absorption is maintained despite a

reduction in urinary calcium.[44] Although conflicting studies have appeared, there are reports of parathyroid stimulation and soft tissue calcification during orthophosphate use.[68]

Even though thiazide was considered to be selective for absorptive hypercalciuria Type I, it may not be ideally indicated. Despite a reduced calcium excretion the intestinal calcium absorption persistently remained elevated.[29] A preliminary study suggests that the retained calcium may be accreted in bone at least during the first few years of therapy.[21] Bone density, determined in the distal third of the radius by photon absorptiometry, increased significantly during thiazide treatment in absorptive hypercalciuria, with an annual increment of 1.34 per cent. In contrast, bone density was not significantly altered[21] in renal hypercalciuria where thiazide was shown to cause a decline in intestinal calcium absorption commensurate with a reduction in urinary calcium.[29] From the practical standpoint the increment in bone density was small and was not associated with any apparent hazard especially since it may be self-limiting. Nevertheless, this preliminary finding suggests that thiazide does not completely satisfy the criteria for selective therapy of absorptive hypercalciuria.

These potential complications of random treatments attest to the value of selective treatments.

Extrarenal manifestations. It is apparent that even if conservative treatments inhibit stone formation, specific treatments may be indicated for the prevention of non-renal complications. Nephrolithiasis should be considered as potentially representing a multisystem disease, in which stone formation is only one of its manifestations. In renal hypercalciuria there may be skeletal involvement, as indicated by a reduced bone density by photon absorptiometry.[46] Selective treatment with thiazide may avert this complication by restoring normal parathyroid function, as shown by stable bone density during a long-term followup.[21] Primary hyperparathyroidism is manifested clinically by peptic ulcer disease and bone disease, as well as by nephrolithiasis. Parathyroidectomy typically averts all three manifestations. Hypokalemia and bone disease may complicate the course of renal tubular acidosis. The treatment with potassium citrate should prevent these complications. Although controversial, there is some evidence that bone may be affected adversely in patients with absorptive hypercalciuria Type III because of hypophosphatemia. Orthophosphate therapy may retard this development.

The impact of improved surgical techniques on the need for selective treatment

The introduction of nephrostolithotomy and extracorporeal shock wave lithotripsy has greatly reduced the moribidity and the cost of removal of renal stones. This improvement has led some to disparage the need for diagnostic evaluation and medical treatment of renal stones. However, there is preponderant evidence to the contrary.

First, the facilitated removal of existing stones does not prevent formation of new stones, whereas selective medical treatments could.

Second, the safety of repeated or multiple stone removals via improved techniques has not been shown. Under the application for the use of extracorporeal shock wave lithotripsy as a medical device in the United States, the FDA disallows multiple application in the same patient.

Third, many patients with existing stones are not candidates for shock wave lithotripsy, e.g. those with numerous small calculi.

Fourth, certain patients with existing stones need not require stone removal. In our experience, the majority of patients with existing stones are asymptomatic when they are under adequate medical therapy. These comments apply particularly to calyceal stones.

Fifth, improved techniques for stone removal do not overcome non-renal manifestations of the disease process previously enumerated.

Conclusion

In conclusion, considerable progress has been made regarding pathogenesis, diagnosis and management of renal stones. The cause for nephrolithiasis can now be determined in nearly 95% of patients, and new stone formation may be prevented in the majority of patients using a variety of selective medical treatments. It is hoped that the validity of selective treatment approach would be forthcoming with a continued understanding of the physicochemical and physiological bases for stone formation, mechanism of drug action and objective assessment of the effects of selective treatments.

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