CONSENSUS CONFERENCE FOR THE METABOLIC DIAGNOSIS AND MEDICAL PREVENTION OF CALCIUM NEPHROLITHIASIS AND ITS SYSTEMIC MANIFESTATIONS
(& Educational course on renal stone disease)

Rome (Italy), March 26 – 28, 2015

Organized by

DIVISION OF NEPHROLOGY AND DIALYSIS
COLUMBUS-GEMELLI UNIVERSITY HOSPITAL
UNIVERSITÀ CATTOLICA DEL SACRO CUORE, ROME, ITALY

Promoted by

FONDAZIONE
INTERNAZIONALE
MENARINI

ABSTRACT BOOK

Palazzo Brancaccio
Viale del Monte Oppio, 7 - Largo Brancaccio, 82/a

CONTENTS

Idiopathic calcium stones: separation from Renal Tubular Acidosis
Is there an incomplete RTA? What is it?

Daniel Fuster
Division of Nephrology, Hypertension and Clinical Pharmacology, University Hospital of Bern, Bern, Switzerland

Distal renal tubular acidosis (dRTA) is a condition characterized by defective urinary acidification in the abscence of reduced GFR. dRTA[1] can be complete, i.e. with sytemic acidosis or incomplete i.e. without systemic acidosis. Complete dRTA is a rare condition in patients with recurrent nephrolithiasis [1]. In contrast, prevalence rates of 2 – 21 % for incomplete dRTA have been reported in the general stone forming population. Incomplete dRTA shares many features of complete dRTA, including hypocitraturia, alkaline urine and hypercalciuria that favor development of Ca stone formation. The typical calculus of dRTA is CaP with a high carbapatite content and a characteristic morphology with a smooth aspect and a glazed brown-yellow appearance with tiny cracks [2]. A very similar stone composition as in dRTA is observed in patients with carboanhydrase inhibitior treatment (acetazolamide, topiramate). As the stone composition changes from CaOx to mixed CaOx-CaP to pure CaP, the prevalence of dRTA increases from 5 to 40% [3].
There are no RCT for the prevention of stones in patients with dRTA. Even RCT for calcareus stones in the abscence of dRTA have not addressed specifically the outcomes of patients with CaP stones. In small studies, treatment with alkali in adults with dRTA decreased hypercalciuria, increased citraturia and reduced stone recurrence [4, 5].
While the diagnosis of complete dRTA is clinically straight forward, incomplete dRTA cannot be discerned by conventional clinical criteria but requires unmasking by a provocative urinary acidification test. Since the original description of 3 patients with incomplete dRTA by Wrong and Davies in 1959, the one day NH_4Cl loading test is considered the gold standard for diagnosis [6].

Several alternative tests with better tolerability or improved safety profile have been described over the years. Due to a lack of rigorous comparative studies, the validity of the different provocative tests used in patients with recurrent nephrolithiasis is currently unknown. In addition, invariant use of „dRTA“ to describe incomplete dRTA *or* complete dRTA further complicates the literature on incomplete dRTA.

But leaving diagnostic issues apart - what is it really, incomplete dRTA ? Unfortunately, despite its clinical relevance in recurrent Ca nephrolithiasis, the pathophysiology of incomplete dRTA remains poorly understood. Some consider it an early («pre-acidotic») version of complete dRTA, others a separate entity. In support of the former, several cases of documented transition from incomplete to complete dRTA have been published and causes of incomplete and complete dRTA overlap (e.g. nephrocalcinosis, Sjögren's syndrome). Unfortunately, systematic longitudinal studies in patients with incomplete dRTA are lacking and we do not know which patients with incomplete dRTA will eventually progress to complete dRTA. Certainly, given the large prevalence difference of the two dRTA forms in recurrent Ca stone formers, transition to complete dRTA must be a rare event.

An important but often neglected difference between complete and incomplete dRTA is that NH_4^+ excretion (and thus net acid excretion) is typically normal in the latter but significantly reduced in the former, supporting the concept of incomplete dRTA as a separate entity. Mechanistically, rate- (or capacity-) limited distal tubular H^+ secretion is the cause for reduced urinary NH_4^+ excretion and high urinary pH in complete dRTA. However, only a gradient-limitation for H^+ secretion or a primary overproduction of NH_4^+ due to proximal tubular cell acidosis can explain high urinary pH, high urinary NH_4^+ excretion and hypocitraturia in the abscence of systemic acidosis as observed in incomplete dRTA [7]. Interestingly, in support of the overproduction hypothesis, some patients with incomplete dRTA seem not to have a gradient limitation for H^+ secretion because urinary pH decreases <5.3 when high urine flow rates are present [8]. Thus, while purely pH based diagnostic criteria suggest homogeneity, incomplete dRTA is likely a heterogeneous entity.

If mechanistic work-up of incomplete dRTA has any prognostic or therapeutic value in recurrent Ca stone formers is currently unknown.
Incomplete dRTA is typically considered an acquired condition, but familial associations have been described e.g. in the case of medullary sponge kidney. We recently demonstrated that heterozygous carriers in a large family with an autosomal-recessive V-ATPase B1 subunit mutation displayed incomplete dRTA accompanied in some family members by recurrent Ca nephrolithiasis [9]. The phenotype in heterozygotes of this peculiar mutation was attributed to haploinsufficiency since *in vitro* studies were not compatible with negative dominance of this mutation. If the other known V-ATPase B1 subunit missense mutations also cause a detectable deficit in urinary acidification in a heterozygous state is currently unknown. Thus, it is conceivable but yet unproven that incomplete dRTA is in part due to allelic variants of genes involved in H^+ secretion in α–intercalated cells.
Clearly, there is a dire need for more clinical and basic studies in the area of incomplete dRTA to better understand and treat this prevalent and clinically relevant condition in patients with recurrent nephrolithiasis.

[1]Unless specified, "dRTA" includes both the complete and incomplete form in this abstract.

References:

1. Pak CY, Britton F, Peterson R, Ward D, Northcutt C, Breslau NA, McGuire J, Sakhaee K, Bush S, Nicar M, Norman DA, Peters P: Ambulatory evaluation of nephrolithiasis. Classification, clinical presentation and diagnostic criteria. *Am J Med* **69**:19-30, 1980.

2. Daudon M, Bouzidi H, Bazin D: Composition and morphology of phosphate stones and their relation with etiology. *Urol Res* **38**:459-467, 2010.

3. Pak CY, Poindexter JR, Peterson RD, Heller HJ: Biochemical and physicochemical presentations of patients with brushite stones. *J Urol* **171**:1046-1049, 2004.

4. Preminger GM, Sakhaee K, Skurla C, Pak CY: Prevention of recurrent calcium stone formation with potassium citrate therapy in patients with distal renal tubular acidosis. *J Urol* **134**:20-23, 1985.

5. Fabris A, Lupo A, Bernich P, Abaterusso C, Marchionna N, Nouvenne A, Gambaro G: Long-term treatment with potassium citrate and renal stones in medullary sponge kidney. *Clin J Am Soc Nephrol* **5**:1663-1668, 2010.

6. Wrong O, Davies HE: The excretion of acid in renal disease. *Q J Med* **28**:259-313, 1959.

7. Donnelly S, Kamel KS, Vasuvattakul S, Narins RG, Halperin ML: Might distal renal tubular acidosis be a proximal tubular cell disorder? *Am J Kidney Dis* **19**:272-281, 1992.

8. Buckalew VM, Jr., McCurdy DK, Ludwig GD, Chaykin LB, Elkinton JR: Incomplete renal tubular acidosis. Physiologic studies in three patients with a defect in lowering urine pH. *Am J Med* **45**:32-42, 1968.

9. Zhang J, Fuster DG, Cameron MA, Quinones H, Griffith C, Xie XS, Moe OW: Incomplete distal renal tubular acidosis from a heterozygous mutation of the V-ATPase B1 subunit. *Am J Physiol Renal Physiol* **307**:F1063-1071, 2014.

Hyperuricosuric Calcium Urolithiasis

Orson Moe, M.D.
University of Texas Southwestern Medical Center, Dallas, TX, USA

The Condition

In 1893, the celebrated surgeon Sir Henry Thomson described mixed calcium oxalate (CaOx) and uric acid (UA) stones amongst his stone collection from mainly men over 60 years of age with cystoliths. Edwin Prien provided the first published account of mixed CaOX/UA stones (1) and together with his son described the occurance of CaOx stones in gouty subjects (2). Gutman and Yü independently offered the same description (3) and suggested that CaOx may trigger UA stones. In 1969, Smith described the converse situation of hyperuricosuria in calcium stone formers (4). The concept of lack of urinary inhibitor rather than excess of components of litholiths was proposed by Dent and Sutor (5). The study that really brought this condition into light was by Coe and Raisen who showed in a small study that calcium stone former with high urine uric acid but not calcium, can successfully be treated by xanthine oxidase inhibition (6). The authors stated that "...these patients may represent a hitherto undescribed syndrome".

The current definition of this syndrome should include the co-existence of calcium (oxalate or phosphate) and uric acid in the stone, the presence of hyperuricosuria, which is in fact not rare in calcium stone formers (7) and the presence or absence of other risk factors for calcium urolithiasis such as hypercalciuria, hyperoxaluria, and hypocitraturia.

Physicochemical Basis

If uric acid causes calcium oxalate stone formation, what are the pathogenic mechanisms that bridge the causality? Three non-mutually exclusive models have been proposed. **A.** In its solid crystalline phase, UA can promote CaOx precipitation by heterogeneous nucleation or epitaxy (8, 9). Hyperuricosuria does increase Na urate concentration product ratio (10) and hyperuricosuria does increase physicochemical CaOx stome risk (reduced formation product ratio) (11). However, the role of heterogeneous nucleation *in vivo* is less uncertain. **B.** Colloidal monosodium urate, and not Na urate crystals from supersaturated

urine may attenuate inhibitor activity against CaOx crystallization (12, 13) but when glycosaminoglycans were specifically examined, uric acid did not affect its inhibitor activity (14). **C.** Another study showed monosodium urate diminishes solubility of CaOx in solution, a process referred to as "salting out" (15, 16). Salting out is also known as antisolvent crystallization, which was classically used to precipitate a non-electrolyte multi-charged macromolecule (most commonly protein) at high electrolyte concentrations (most commonly ammonium sulfate). The mechanisms by which Na urate "salt-out" calcium oxalate still needs to be defined.

Therapy

Despite this controversy in mechanism, clinical studies in HUCU patients have shown a significant decline in the rate of recurrent kidney stone formation in those treated with xanthine oxidase inhibition. The first study which was not placebo-controlled was performed by Coe and Raisen in 1973 where stone event frequency in calcium stone formers with hyperuricosuria but not hypercalciuria, was drastically diminished by allopurinol compared to the subjects' history (17). A randomized controlled trial was published in 1997 by Smith which has been cited both as a "negative" and "positive study (18); in the sense that Allopurinol did not improve clinical stone events overall but did drastically reduced "stone-free status." In contrast to the study by Coe and Raisen, this study used a mixed group of stone formers who had hyperuricemia rather than hyperuricosuria and alkali was given to increase urine pH to > 6.5; which will greatly increase Na urate in the urine (18). A landmark study was done by Coe where patients were well classified in terms of hypercalciuria, hyperuricosuria, or both, and therapy was tailored thiazide, allopurinol, or both (17). The clinical benefit of this study was very clear. One last study was by Ettinger in 1986, where patients with hyperuricosuria and no or modest hypercalciuria was treated with allopurinol and the stone event-free rate was increased from 40 to 70% (19). A non-purine xanthine oxidase inhibitor analog, febuxostat, has recently been approved for the treatment of hyperuricemia associated with gouty arthritis.

In a retrospective study, the use of febuxostat in patients with gout with allergies to allopurinol was shown to be a safe alternative (14). In a 6 month, double-blind RCT, hyperuricosuric calcium stone formers

were treated with 80 mg/day of febuxostat, 300 mg/day of allopurinol or placebo. Febuxostat reduced 24-hour urinary uric acid significantly more than allopurinol but there was no change in stone size or number over this period of time (15).

Questions to be Addressed.

There are some important clinically questions that are in need of answers.

1. Does the condition HUCU exists? Based on epidemiologic data should lack of correlation between urinary uric acid and stone risk (20, 21), some have question the legitimacy of this condition. Should this be further debated?

2. Hyperuricosuria – dose-relationship to stone risk? Using formation product ratio of CaOx as a surrogate, the effect of activity product ratio of Na urate appears to be continuous with no inflection point (11).

3. Interaction with other risks? There is no doubt that the effect of uric acid/urate is modified by the levels of calcium, oxalate, citrate, and water. It may be challenging to incorporate these factors into the interpretation of urinary uric acid as a stone risk. Perhaps an in silo model akin to EQUIL or JESS can be helpful.

4. True physicochemical basis? This is still very much in debate and understanding these issues will help the elucidation of pathophysiology and design of treatment.

5. Who to treat?

6. Target of lowering? The last two questions are more pragmatic for practitioners and we will attempt to arrive at a consensus at the meeting.

References:

1. Prien EL, Frondel C. Studies in urolithiasis; the composition of urinary calculi. The Journal of urology. 1947;57(6):949-94. PubMed PMID: 20243909.

2. Prien EL, Prien EL, Jr. Composition and structure of urinary stone. The American journal of medicine. 1968;45(5):654-72. PubMed PMID: 4301160.

3. Gutman AB, Yu TF. Uric acid nephrolithiasis. The American journal of medicine. 1968;45(5):756-79. PubMed PMID: 4879835.

4. Smith MJ, Hunt LD, King JS, Jr., Boyce WH. Uricemia and urolithiasis. The Journal of urology. 1969;101(5):637-42. PubMed PMID: 5780596.

5. Dent CE, Sutor DJ. Presence or absence of inhibitor of calcium-oxalate crystal growth in urine of normals and of stoneformers. Lancet. 1971;2(7728):775-8. PubMed PMID: 4106603.

6. Coe FL, Raisen L. Allopurinol treatment of uric-acid disorders in calcium-stone formers. Lancet. 1973;1(7795):129-31. PubMed PMID: 4118468.

7. Coe FL. Hyperuricosuric calcium oxalate nephrolithiasis. Kidney international. 1978;13(5):418-26. PubMed PMID: 661071.

8. Pak CY, Arnold LH. Heterogeneous nucleation of calcium oxalate by seeds of monosodium urate. Proceedings of the Society for Experimental Biology and Medicine Society for Experimental Biology and Medicine. 1975;149(4):930-2. PubMed PMID: 241081.

9. Coe FL, Lawton RL, Goldstein RB, Tembe V. Sodium urate accelerates precipitation of calcium oxalate in vitro. Proceedings of the Society for Experimental Biology and Medicine Society for Experimental Biology and Medicine. 1975;149(4):926-9. PubMed PMID: 241080.

10. Pak CY, Waters O, Arnold L, Holt K, Cox C, Barilla D. Mechanism for calcium urolithiasis among patients with hyperuricosuria: supersaturation of urine with respect to monosodium urate. The Journal of clinical investigation. 1977;59(3):426-31. doi: 10.1172/JCI108656. PubMed PMID: 14173; PubMed Central PMCID: PMC333378.

11. Pak CY, Barilla DE, Holt K, Brinkley L, Tolentino R, Zerwekh JE. Effect of oral purine load and allopurinol on the crystallization of calcium salts in urine of patients with hyperuricosuric calcium urolithiasis. The American journal of medicine. 1978;65(4):593-9. PubMed PMID: 707519.

12. Pak CY, Holt K, Zerwekh JE. Attenuation by monosodium urate of the inhibitory effect of glycosaminoglycans on calcium oxalate nucleation. Investigative urology. 1979;17(2):138-40. PubMed PMID: 468513.

13. Roberston W, Peacock M. Urinary acid mucopolysaccaride inhibitors of Ca oxalate crystallization. In: Fleisch H, Smith L, Vahlensiec W, editors. Urolithiasis Clinical and Basic Research. New York, NY: Plenum Press; 1978. p. 331-8.

14. Grover PK, Ryall RL, Marshall VR. Calcium oxalate crystallization in urine: role of urate and glycosaminoglycans. Kidney international. 1992;41(1):149-54. PubMed PMID: 1593851.

15. Grover PK, Ryall RL. Urate and calcium oxalate stones: from repute to rhetoric to reality. Mineral and electrolyte metabolism. 1994;20(6):361-70. PubMed PMID: 7783698.

16. Kallistratos G, Timmermann A, Fenner O. [Influence of the salting-out effect on the formation of calcium oxalate crystals in human urine]. Die Naturwissenschaften. 1970;57(4):198. PubMed PMID: 5446710.

17. Coe FL. Treated and untreated recurrent calcium nephrolithiasis in patients with idiopathic hypercalciuria, hyperuricosuria, or no metabolic disorder. Annals of internal medicine. 1977;87(4):404-10. PubMed PMID: 907239.

18. Smith MJ. Placebo versus allopurinol for renal calculi. The Journal of urology. 1977;117(6):690-2. PubMed PMID: 875139.

19. Ettinger B, Tang A, Citron JT, Livermore B, Williams T. Randomized trial of allopurinol in the prevention of calcium oxalate calculi. The New England journal of medicine. 1986;315(22):1386-9. doi: 10.1056/NEJM198611273152204. PubMed PMID: 3534570.

20. Curhan GC, Willett WC, Speizer FE, Stampfer MJ. Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. Kidney international. 2001;59(6):2290-8. doi: 10.1046/j.1523-1755.2001.00746.x. PubMed PMID: 11380833.

21. Curhan GC, Taylor EN. 24-h uric acid excretion and the risk of kidney stones. Kidney international. 2008;73(4):489-96. doi: 10.1038/sj.ki.5002708. PubMed PMID: 18059457.

Which Stone Patient is at High Risk of CKD?

Gambaro Giovanni
Catholic University of the Sacred Heart, Columbus University Hospital, Department of Nephrology and Dialysis, Rome, Italy

Renal stone formers from the general population have about a two-fold higher risk for decreased renal function or need for renal replacement therapy.
This risk seems to be independent of risk factors for CKD that are common in stone formers such as hypertension and diabetes mellitus. Those who are female and overweight are at risk, together with those having frequent UTI or struvite stones. Stone formers with urinary malformations and urinary diversion, or malabsorptive bowel, or genetic disorders have a particularly high risk of CKD/ESRD.
Non invasive or mini-invasive urological interventions for stones do not impact unfavorably on function. When this occurs it is most likely due to the primary conditions needing repeated surgeries rather than to surgeries themselves.
Although the effect size is modest, nephrolithiasis should be viewed as a condition which may lead to chronic kidney disease.
Thus, in patients with renal stones the evaluation of the global risk of developing CKD/ESRD is mandatory.

Which stone patient is at high risk of bone disease?

David A. Bushinsky, MD
Chief, Nephrology Division, University of Rochester Medical Center, Rochester, NY, USA

Hypercalciuria is the most common metabolic abnormality found in patients with calcium-containing kidney stones. Patients with hypercalciuria often excrete more calcium than they absorb, indicating a net loss of total body calcium. The source of this additional urine calcium is almost certainly the skeleton, the largest repository of calcium in the body. Hypercalciuric stone formers exhibit decreased bone mineral density (BMD) and the decrease is correlated with the increase in urine calcium excretion. The decreased BMD also correlates with an increase in markers of bone turnover, as well as increased fractures.

In humans, it is difficult to determine the cause of the decreased BMD in hypercalciuric stone formers. To study the effect of hypercalciuria on bone we utilized our genetic hypercalciuric stone-forming (GHS) rats which were developed through successive inbreeding of the most hypercalciuric Sprague-Dawley rats. The GHS rats excrete significantly more urinary calcium than similarly fed controls and all the GHS rats form kidney stones while control rats do not. The hypercalciuria is due to a systemic dysregulation of calcium homeostasis, with increased intestinal calcium absorption, enhanced bone resorption and decreased renal tubular calcium reabsorption. There is an increase in vitamin D receptors in all these target tissues. We recently found that GHS rats fed an ample calcium diet have reduced BMD and their bones are more fracture prone, indicating an intrinsic disorder of bone not secondary to diet. Administration of the thiazide diuretic, chlorthalidone, to GHS rats led to a significant increase in bone quality with a far smaller increase in bone density. In GHS rats fed a low calcium diet bisphosphonates markedly decreases urine calcium excretion.

In stone forming humans it is far more difficult to test interventions that will lead to an increase in bone mass and quality as bone only slowly changes its mass.

Patients with hypercalciuria, especially those who are at increased risk for osteoporosis, should have bone mass determined by DEXA.
If bone mass is low there are few controlled studies in hypercalciuric stone formers to guide therapy; however, there is a wealth of data in patients with osteoporosis to guide therapy. In hypercalciuric stone formers there is general agreement that patients should consume a relatively low sodium and protein diet which will decrease hypercalciuria. Patients should consume an age and gender appropriate amount of dietary calcium and should be 25 hydroxyvitamin D replete. Pharmacologic therapy that is directed at reducing recurrent stone formation may also help stabilize bone density. Thiazide diuretics lower urinary calcium and decrease recurrent stone formation and may increase bone density. Alkali decreases bone resorption, especially in patients eating a high animal protein diet, and may not only decrease urine calcium excretion and reduce recurrent stone formation but improve bone mass as well. Bisphosphonates and denosamab decrease urine calcium excretion, decrease bone resorption, effectively stabilize bone mass and decrease fracture.

A stone episode can often be rapidly treated while a fracture in a hypercalciuric stone former may lead to lifetime morbidity and increased mortality. Randomized controlled studies to test therapies aimed at improving bone quality in hypercalciuric stone formers are clearly needed and should be a high priority in our patients.

References:

1. Krieger, NS and DA Bushinsky. The Relation Between Bone and Stone Formation. Calcifi Tissue Int. 93: 374, 2013.

2. Fink HA et al. Medical Management to Prevent Recurrent Nephrolithaisis in Adults: A Systematic Review for an American College of Physicians Clinical Guideline. Ann Intern Med 158: 535, 2013.

3. Sakhaee K. Nephrolithiasis-Associated Bone Disease: Pathogenesis and Treatment Options. Kidney Intl 79: 393, 2011.

4. Melton III LI et al. Gracture risk among patients with Urolithiasis: A Population-Based cohort study. Kidney Intl. 53: 459, 1998.

5. Pak CY et al. Prevention of stone formation and bone loss in absorptive hypercalciuria by combine dietary and pharmacological interventions. J. Urol, 169, 464, 2003.

Can we measure upper Limits of Metastability for Practical Use?

Is supersaturation a guide to stone treatment - what are the goals. What is the best intermediate outcome measure when SS is not available (as in most of Europe). Disorders that promote supersaturation - can be measured? Importance for treatment outcome. Importance for predicting comorbidities? Importance for future research?Importance for planing trials?

Martino Marangella, M.M.
Mauriziano Hospital, Turin (Italy)

It is well known that an essential condition for a stone to form is urine environment be supersaturated with a given component of stones. This condition is probably sufficient in case of non calcium-containing renal stones, including struvite, cystine and, may be, uric acid stones. Conversely, calcium oxalate (CaOx) and calcium phosphate (CaP) supersaturation (SS) does not always explain calcium stone formation, as can be deduced by the fact that most of non-stone forming individuals have supersaturated urines. To explain this unexpected behavior, metastability and/or inhibitors are generally put forward. Upper limit of metastability (ULM) denotes the experimental value of SS whereby spontaneous nucleation occurs: the higher the ULM the lower the risk of forming stones at a given SS. ULM for both CaOx and CaP were assessed in both stone forming patients (SF) and normals (N) of both sexes [1, 2], in pediatric age [3] and in different series, at baseline and after any treatment. In the majority of cases a surprising close relationship was found between SS and ULM for CaOx > CaP, and treatment did not significantly alter ULM/SS ratio [4, 5]. Moreover, the distance between ULM and SS tended to be lower in SF, especially for CaP. Citrate concentration was found to be directly related to ULM for both CaOx and CaP [2, 6]. However slopes of relationships and citrate excretion between SF and N overlapped, leading to conclusion that citrate may not fully explain differences between N and SF. Because ULM is only an index of crystal nucleation, research was extended to growth, aggregation and cell adhesion of crystals, with controversial results comparing

calcium SF to N and males to females [2, 7]. Many reasons are put forward to explain such discrepancies, including differences in group composition, small number of individuals enrolled, different assays, use of diluted and not whole urine.

Based on the so far available data and considering that methods for assessing ULM and crystal growth and aggregation are time consuming procedures, they are not routinely carried out, if not in dedicated laboratories and for experimental studies. Conversely, the idea to estimate state of saturation by measuring activity product ratio (ß) has more successfully expanded [8]. Ab initio calculations have allowed a wider routinely use of these measurements in the management of patients with stones and today, computer based calculation programs are commercially available [9, 10]. However, their use is somehow hampered by the need of several urinary parameters, whose availability is not always easy to obtain in hospital laboratories. Simplified approach to state of saturation have therefore been proposed in the form of nomograms or simplifies formulas [11, 12]. It is however indisputable that any approach aimed at evaluating stone risk cannot omit some variable, which must be held as strong, including calcium magnesium phosphate oxalate citrate for calcium stones, pH and urate for uric acid stones, and of course relevant chemistries for rarer stones. But, we maintain that estimating ß, whatever method is used, is a highly recommendable tool to assess the overall stone forming potential of urine.

The issue to be discussed is now what ß does and what does not. Starting from the latter point, it can be agreed that it is unable to discriminate between N and SF (but virtually no published assay does so), does not inform on inhibitory potential of urine, does not explain the cells-crystal interactions in the renal tubule. Conversely, it is an essential condition for crystal to form and grow, evaluates overall lithogenic potential, it is useful in the management of SF forming patients and represents an easy to use and repeatable risk score. In clinical follow-up of SF undergoing any treatment, ß assesses efficacy better than measurements of single urine components and may concur to prevent untoward effects of therapy. Moreover, while measuring excretion of relevant ions requires timed urine collection, estimating ß can be carried out also in spot urines, and this can be especially useful

in pediatric patients or to study circadian variations of stone risk. Another use of ß comes from the observed good relationship between ß and stone composition [13]. Thus ß can help to diagnose type of stone disease in case stones or fragments are not available for analysis. In some cases excessively high ß leads to suspect nephrolithiasis secondary to defined diseases such as renal tubular acidosis for ß brushite, primary or secondary hyperoxaluria for ß CaOx. Finally, in experimental studies or in clinical trials, estimating ß appears to better complete the related designs.

References:

1. Nicar MJ et al. A simple technique for assessing the propensity for crystallization of calcium oxalate and brushite in urine from the increment in oxalate or calcium necessary to elicit precipitation. Metabolism. 1983; 32: 906-10.

2. Asplin JR et al. Reduced crystallization inhibition by urine from women with nephrolithiasis. Kidney Int. 2002;61:1821-9.

3. Bergsland KJ et. Urine risk factors in children with calcium kidney stones and their siblings. Kidney Int. 2012; 81: 1140-8.

4. Asplin JR et al. Dependence of upper limit of metastability on supersaturation in nephrolithiasis. Kidney Int. 1997;52: 1602-8.

5. Borghi L. Relationship between supersaturation and calcium oxalate crystallization in normals and idiopathic calcium oxalate stone formers. Kidney Int. 1999;55:1041-50.

6. Nicar MJ et al. Inhibition by citrate of spontaneous precipitation of calcium oxalate in vitro. J Bone Miner Res. 1987; 2: 215-20.

7. Asplin JR. Reduced crystallization inhibition by urine from men with nephrolithiasis. Kidney Int. 1999; 56:1505-16.

8. Robertson WG et al. Activity products in stone-forming and non-stone-forming urine. Clin Sci. 1968;34:579-94.

9. Werness PG et al. Equil 2: A basic computer program for the calculation of urinary saturation. J Urol 1985; 134:1242-4.

10. Marangella M et al. LithoRisk: A software for calculating and visualising nephrolithiasis risk profiles. G Ital Nefrol. 2002;19:693-8.

11. Marshall RW et a. Nomograms for the estimation of the saturation of urine with calcium oxalate, calcium phosphate, magnesium ammonium phosphate, uric acid, sodium acid urate, ammonium acid urate and cystine. Clin Chim Acta. 1976;72:253-60.

12. Tiselius HG. An improved method for the routine biochemical evaluation of patients with recurrent calcium oxalate stone disease. Clin Chim Acta. 1982;122:409-18.

13. Asplin J. Supersaturation and stone composition in a network of dispersed treatment sites. J Urol. 1998;159:1821-5.

Use of surgical observations for diagnosis

James E. Lingeman, M.D., FACS
Indiana University School of Medicine, Indianapolis, USA

Use of thorough endoscopic observation, especially with digital technology, of the appearance of the renal papillae during percutaneous and ureteroscopic stone removal has lead to important insights about the initiating events of stone formation. Our current understanding of stone pathogenesis suggests three main pathways for stone formation: calcium oxalate overgrowth on interstitial deposits of hydroxyapatite, so called Randall's plaque (Type 1); crystal deposits in the inner medullary collecting ducts and ducts of Bellini; and finally stone formation in free solution.

Calcium oxalate overgrowth on Randall's plaque is the predominant pathway for so-called idiopathic calcium oxalate stone formers. In idiopathic calcium oxalate stone formers, although on average only 7% of the papillary surface is covered with Randall's plaque, over 75% of attached stones are found to be attached to Randall's plaque. In this characteristic stone phenotype, unattached stones also show evidence of Randall's plaque when examined by micro CT, a powerful non-destructive tool for stone analysis. The degree of papillary surface coverage of Randall's plaque correlates directly with urine calcium and inversely with urine volume and pH. No correlation has been documented with urine citrate, oxalate, or magnesium excretion. Clinical stone activity also correlates directly with the percent coverage of the renal papillae with Randall's plaque further attesting to the significance of these deposits in idiopathic calcium oxalate stone formers. Randall's plaque is observed in other stone-forming phenotypes who have either hypercalciuria (primary hyperparathyroidism, distal renal tubular acidosis, calcium phosphate, and brushite stones) or low urine volume (ileostomy). Importantly, in idiopathic calcium oxalate stone formers, crystal deposits are not found in the inner medullary collecting ducts or ducts of Bellini.

Crystal deposits in inner medullary collecting ducts and ducts of Bellini are a prominent feature of numerous other less common stone phenotypes (calcium phosphate and brushite stones, primary hyperparathyroidism, distal renal tubular acidosis, ileostomy, enteric hyperoxaluria, cystinuria). The endoscopic appearance of papillae harboring such deposits differs dramatically from idiopathic calcium oxalate stone formers with Randall's plaque. These inner medullary collecting ducts and ducts of Bellini deposits are associated with significant damage to the renal papillae and the resultant inflammation and fibrosis are reflected in specific endoscopic features such as Randall's plaque type 2 (yellow plaque), duct of Bellini dilation, papillary erosion and retraction. These endoscopic findings imply a more significant type of disease vis-à-vis papillary function. No matter the stone phenotype, inner medullary collecting duct and duct of Bellini deposits often contain hydroxyapatite suggesting damage to the acidification mechanism of the papillae.

Careful surgical observation is also important in distinguishing calculi from nephrocalcinosis for renal calcifications noted on imaging. This distinction cannot be made reliably by current imaging techniques including CT. Nephrocalcinosis is far more common than is appreciated by clinicians and radiologists. We will present evidence that nephrocalcinosis exists in approximately 70% of calcium phosphate and brushite patients who do not have evidence of systemic disease (primary hyperparathyroidism, distal renal tubular acidosis, medullary sponge kidney disease).

Additionally, endoscopic observation will detect many small stones beyond the ability of CT to document. It seems plausible (and testable) that such small stones would eventually grow to clinical significance. These small incidentally noted calculi are easily removed at the time of treatment of the symptomatic stone.

There are also rare but important stone phenotypes such as primary hyperoxaluria which may be suspected by endoscopic and clinical circumstances alone (i.e. calcium oxalate stones in the absence of

enteric hyperoxaluria with dilated ducts of Bellini with stones and no Randall's plaque).

Finally, a proposed scheme will be presented for documenting the extent of papillary changes so as to enhance communication and research in this area.

References:

1. Evan AP, Lingeman JE, Coe FL, Parks JH, Bledsoe SB, Shao Y, Sommer AJ, Paterson RF, Kuo RL, and Grynpas M. Randall's plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle. *The Journal of Clinical Investigation* 111(5):607-616, March 2003.

2. Kuo RL, Lingeman JE, Evan AP, Paterson RF, Parks JH, Bledsoe SB, Munch LC, and Coe FL. Urine calcium and volume predict coverage of renal papilla by Randall's plaque. *Kidney Intl*, 64(6):2150-2154, December 2003.

3. Zarse CA, McAteer JA, Sommer AJ, Kim SC, Hatt E, Lingeman JE, Evan AP, and Williams JC Jr. Non-destructive analysis of urinary calculi using micro computed tomography. *BMC Urology* 4(1):15, December 2004.

4. Kim SC, Coe FL, Tinmouth WW, Kuo RL, Paterson RF, Parks JH, Munch LC, Evan AP, Lingeman JE. Stone formation is proportional to papillary surface coverage by Randall's plaque. *J Urol* 173(1):117-119, January 2005.

5. Evan AP, Coe FL, Lingeman JE, Shao Y, Sommer AJ, Bledsoe SB, Anderson JC, Worcester EM. Mechanism of formation of human calcium oxalate renal stones on Randall's plaque. *The Anatomical Record* 290:1315-1323, October 2007.

6. Miller NL, Gillen DL, Williams, Jr. JC, Evan AP, Bledsoe SB, Coe FL, Worcester EM, Matlaga BR, Munch LC, Lingeman JE. A formal test of the hypothesis that idiopathic calcium oxalate stones grow on Randall's plaque. *BJU Intl* 103:966-971, April 2009, [PMCID: PMC3459677].

7. Miller NL, Williams Jr. JC, Evan AP, Bledsoe SB, Coe FL, Worcester EM, Munch LC, Handa SE, Lingeman JE. In idiopathic calcium oxalate stone formers, unattached stones show evidence of having originated as attached stones on Randall's plaque. *BJUI*, 105:242-245, January 2010, [PMID:19549258], [PMC2807918].

8. Coe FL, Evan AP, Lingeman JE, Worcester EM. Plaque and deposits in nine human stone diseases. *Urol Res* 38(4):239-247, August 2010, [PMID:20625890].

9. Evan AP, Lingeman JE, Worcester EM, Sommer AJ, Phillips CL, Williams JC, Coe FL. Contrasting histopathology and crystal deposits in kidneys of idiopathic stone formers who produce hydroxyapatite, brushite, or calcium oxalate stones. *Anat Rec* 297(4):731-748, April 2014.

What does the Urologist ask the Nephrologist?

Noor Buchholz
London, UK

Nephrologists and Urologists have been working next to each other for a very long time. Yet, too often there seems to be a rivalry, almost a competition as can be found in many places between physicians and surgeons. Naturally, given the different approaches to disease, their view of the world and even their "dialect" differ. This poses a barrier between the two specialties that often care for the same patients, the same organ, and the same pathophysiologies.

This applies also to stone disease, which is often complex and caused by underlying co-morbidities that cannot be tackled by blasting the stone alone. Conveniently though for the urologists, developments in stone blasting technologies have made treatment very smooth and easy, leading to a neglect of the diagnosis of underlying causes. On the other hand, nephrologists show only a limited interest in stone disease amongst all the other renal pathologies to deal with.

If we ask the question "what does the urologist ask the nephrologist" then we must keep all this in mind.

Often, the question is also not "what to ask" but "when to ask". When should be the right time in the course of a disease to involve the nephrologist?

Areas of overlap related to stone disease where a co-operation may be required could be renal function, urinary findings such as haematuria and proteinuria, kidney scarring, metabolic stone disease and surgery on single or impaired kidneys.

As far as renal function (creatinine, eGFR) and urinary findings are concerned, the questions that may be asked by the urologist may be at "what level", at "what point in time" or "when is there no need" to refer. Kidney scars may also give rise to the question of pain management. Metabolic stone disease of course rises all the questions about whom to investigate, how much and how often, how to treat and when to follow up (which is the topic of another working group). Finally, surgery on single kidneys poses a risk for renal impairment which the nephrologist should be alerted of.

We are not aware of any guidelines for urologists for nephrology referrals. There are guidelines out there for General Practitioners. However, few studies in the literature show a poor implementation as we may assume to be true for urologists as well.
Searches on Pubmed and Google for such guidelines using an array of search terms did not reveal any hits.
We send out an email questionnaire to 523 addresses and got 14.5% responses back. The average response rate to monkey surveys of all kinds as published on their website is 24.8%. The low response rate may have been confounded by invalid email addresses, but it may also reflect a relatively low interest in complex stone disease although these emails have been targeted at delegates from former stone conferences.
Of the ones that did respond, 74.5% worked in major hospitals. 77% were well experienced urologists with more than 10 clinical years under their belt.
90% had a nephrology service available in their hospital, but only 37% stated a declared interest in stone disease from the side of the nephrologist. On the other hand, 51% clearly stated a lack of interest.
Looking at the number of stone patients seen, it becomes clear that the interest on the side of the urologists is not necessarily linked to the stone patient volume.
What is now the actual referral practice amongst our responders? 51% of urologists refer occasionally, but more worryingly, 39% never do so. Of those who do refer, 66% refer between 1 and 10 patient per month. There is however light at the end of the tunnel in the stone field as secondary and metabolic stone disease make up 60% and 48% of these referrals, respectively.
We put forward some key topics where referral guidance seems to be crucial based on the GP referral guidelines mentioned earlier.
It is important that urologists and nephrologists speak the same language, that is use the same criteria and measuring tools, and define their interpretation in the same way.
For example, when asked how they assess renal function, 43% use the creatinine only, whereas 51% correctly would use eGFR. Urologists need to know when to refer immediately, urgently, or when a referral can wait or is not needed at all.

They also need to know what defines stage 1-5 renal impairment, and how to follow those patients up when they are seen in the urology clinic.
It should be clear when a haematuria or proteinuria warrants referral.
Renal scars need to be defined and referral criteria need to be established. Agreement between the two specialties about when to involve the pain team should be reached in a standardized fashion.
As metabolic stone disease is concerned, of course in an ideal world this should be dealt with by a combined clinic, also involving dieticians and lifestyle coaches. Urologists must be aware and guided as to what diseases pose a risk for underlying systemic disease, frequent stone recurrence, CKD and bone disease.
From our experience, many urologists will have an unclear picture about MSK and nephrocalcinosis. Definitions and knowledge of risk factors will help them to treat and refer properly.
In our questionnaire, we identified some particular areas of discrepancies that need to be addressed in such guidelines.
These refer to the further diagnosis and follow-up of simple renal cysts, awareness of proteinuria hidden amongst other more obvious findings, kidney function in diabetics, definition of worsening renal impairment, interpretation of 24h urines, renal imaging (when and what), surgical cut-off for afunctional kidneys, use of DEXA scan, cardiovascular risk in conjunction with renal impairment, and metabolic syndrome.
Our task will be to raise awareness, provide guidance and promote co-operation between urologists and nephrologists.

What the Nephrologist asks the Urologist.
Developing a guideline for interaction and joint follow-up

E. Croppi
University of Florence, A.S.L. 10 Florence, Florence, Italy

In the clinical management of patients with nephrolithiasis, the collaboration between urologist and nephrologist is crucial.
Despite this, aspects of an integrated nephro-urological management of kidney stones have so far had little attention from the literature and, nowadays, there are no guidelines regarding this important topic.
Often the relationship between the nephrologist and urologist is "alternative" rather than "complementary" in the context of the two main clinical presentations of the disease:

Acute phase (colic)
Especially in the case of urinary tract obstruction, the urologist often takes the lead deciding for the surgical removal of the kidney stone in order to resolve the acute event.
In uncomplicated cases, the nephrologist usually intervenes subsequently to set diagnostic evaluation and to prescribe therapies aimed at preventing the recurrence of the disease.
Conversely, in case of acute decompensated renal failure, e.g. because of single kidney or bilateral obstruction or in case of sepsis, a prompt nephrological intervention may be necessary in order to remedy life-threatening conditions, like electrolyte disturbance or fluid overload.
- Clinical stability phase (occasional findings of nephrolithiasis, or persistent/residual kidney stone remaining after the acute phase).
During this clinical situation, often the nephrologist is consulted first in order to avoid the recurrence of the disease, and the surgical evaluation will take place afterward. The evaluation of indications, timing and methods for a possible surgical approach to the disease may require both the nephrologist and the urologist.
In both these clinical scenarios the cooperation between the nephrologist and urologist is necessary.

It takes into account the complexity of the patient as a whole, as well as the perspectives offered by the medical and/or surgical approach for the most convenient choice.

In these clinical contexts: "what does the nephrologist ask the urologist?"
Specific questions in these cases should include the key points summarized below:

1) *Before elective surgery,* a careful assessment of the etiology of renal stones should be performed, in order to prevent sudden relapses in secondary forms of nephrolithiasis (i.e., in primary hyperparathyroidism).

2) *In patients with advanced renal failure,* renal surgery may produce unfavorable outcomes on the residual renal function and cause dialysis-dependent end stage renal disease. With those patients, nephrologist and urologist should collaborate in the evaluation of the risk-benefit ratio of the intervention.

3) *Get hold of the available fragments* of the stone.

4) *Provide a reliable analysis* of the stone (e.g. infrared spectroscopy, x-ray diffraction and polarization microscopy).

5) *Submit all patients to first level biochemical evaluation,* which can be performed even in acute cases, to exclude some of the non idiopathic forms of the disease (i.e. hypercalcemic syndromes).

6) *Advise the patient with severe disease, or those with putative high risk of recurrence, of the need for a comprehensive metabolic study*.

7) In the case of infected stones, *completely render the kidney stone free*, given the high probability of a recurrence due to residual fragments.

8) In the case of uric acid and cistine nephrolithiasis, *explore the possibility of pharmacological litholisis,* alternative or complementary to surgery.

9) Metabolic abnormalities have also been described also in stone formers with urinary tract abnormalities. Therefore, the investigations on metabolic risk factors may also be useful also in those patients.

Moreover, as a part of integrated clinical management of a nephrolithiasic patient, the nephrologist and urologist also have to face other issues, such as:

1) *Quality and cost/benefit ratio* of the protocols of laboratory investigations of renal stone forming patients.

2) *Cost/benefit analysis* of instrumental investigations for the follow-up of renal stone forming patients (economic cost, radiologic risk).

Defining metabolic activity of nephrolithiasis.
Appropriate evaluation and follow-up of stone formers

Adam G. Kaplan, Glenn M. Preminger, Pietro Manuel Ferraro, Antonio Nouvenne, Andrea Tasca and Ita P. Heilberg
Duke Comprehensive Kidney Stone Center, Division of Urologic Surgery, Duke University Medical Center, Durham, North Carolina, USA
and
Federal University of São Paulo (UNIFESP), São Paulo, Brazil

Introduction
The metabolic evaluation and medical management of kidney stone disease varies widely, based on several patient and practitioner-related factors. The purpose of this document is to provide consensus guidelines for appropriate evaluation and follow-up of stone formers based on metabolic stone activity and imaging studies.

Methods
A systematic review of the literature was performed to identify prospective and well-performed retrospective studies of metabolic evaluation and follow-up of patients with nephrolithiasis. The authors then graded the evidence and developed consensus recommendations related to the questions: How do we define the metabolic activity of nephrolithiasis? Is there a difference between single or recurrent stone formers and how are they defined? How should kidney stone patients be followed – metabolically / radiographically?

Results
The panel agreed that both single stone formers and recurrent stone formers have similar metabolic profiles, and there is no way to accurately predict recurrence based on metabolic analysis alone. Other established epidemiological tools allow for a distinction between patients at low-risk or high-risk for recurrence. Additionally, periodic imaging allows for an assessment of metabolic activity, defined as new stone formation or stone growth.

For patients at high risk for recurrence based **on risk factors or metabolic activity, t**he full metabolic evaluation for the baseline metabolic profile should be obtained at least 3-4 weeks after the last stone passage or treatment. Patients undergoing metabolic evaluation should be unobstructed, eating their regular diet and without urinary tract infection. **The panel recommends that two 24-hour urine studies on a random diet should be collected on consecutive or within 3 non-consecutive days to complete a comprehensive metabolic evaluation.** Another 24-hour urine should be repeated after 3-4 months on selective medical therapy (within 6 months) from the beginning of treatment, to assess response to dietary and/or medical therapy or adverse effects. Follow-up thereafter can be yearly to assess the effectiveness and adherence of metabolic therapy. Previous investigations suggest that imaging studies, should be typically performed every 1 to 2 years, though the timing and type of imaging can be tailored based on stone activity, clinical signs/symptoms and stone location (renal or ureteral).

Conclusions

Single and recurrent stone formers share many similarities in metabolic profiles. Based on an assessment of risk for stone recurrence and metabolic activity, the single and recurrent stone formers should be evaluated comprehensively, including two 24-hour urine studies on a random diet. Targeted medication and dietary advice is effective for many patients in reducing the risk of stone recurrence. Follow-up of those with stone disease should be obtained depending on the level of metabolic activity of the patient. A standard scheme includes a baseline metabolic profile, a repeat study 3-6 months after initiation of treatment, and then yearly when stable, with abdominal imaging obtained every 1-2 years.

References:

1. Gambaro G, Reis-Santos JM, Rao N. Nephrolithiasis: Why Doesn't Our "Learning" Progress? Eur Urol. 2004 May;45(5):547-56.

2. Rule AD, Lieske JC, Li X, Melton LJ, Krambeck AE, Bergstralh EJ. The ROKS Nomogram for Predicting a Second Symptomatic Stone Episode. J Am Soc Nephrol. 2014 Dec 1;25(12):2878-86.

3. Fink HA, Wilt TJ, Eidman KE, Garimella PS, MacDonald R, Rutks IR, et al. Recurrent Nephrolithiasis in Adults: Comparative Effectiveness of Preventive Medical Strategies [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012 [cited 2015 Mar 1]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK99762/

4. Pearle MS, Goldfarb DS, Assimos DG, Curhan G, Denu-Ciocca CJ, Matlaga BR, et al. Medical management of kidney stones: AUA guideline. J Urol. 2014;192(2):316-24.

5. Bensalah K, Tuncel A, Raman JD, Bagrodia A, Pearle M, Lotan Y. How Physician and Patient Perceptions Differ Regarding Medical Management of Stone Disease. J Urol. 2009 Sep;182(3):998-1004.

5. Heilberg IP, Goldfarb DS. Optimum Nutrition for Kidney Stone Disease. Adv Chronic Kidney Dis. 2013 Mar;20(2):165-74.

6. Eisner BH, Goldfarb DS. A Nomogram for the Prediction of Kidney Stone Recurrence. J Am Soc Nephrol. 2014 Dec 1;25(12):2685-7.

7. Fulgham PF, Assimos DG, Pearle MS, Preminger GM. Clinical Effectiveness Protocols for Imaging in the Management of Ureteral Calculous Disease: AUA Technology Assessment. J Urol. 2013 Apr;189(4):1203-13.

When to use Citrate?

Khashayar Sakhaee, MD
Department of Internal Medicine, Charles and Jane Pak Center for Mineral Metabolism and Clinical Research, Dallas, USA

Potassium citrate (KCit) was introduced in 1983 as a treatment for calcium nephrolithiasis. Citrate is now widely used either alone or in combination with thiazide or thiazide analogue diuretics for the treatment of calcium nephrolithiasis. Recently, it has been suggested that KCit may increase the risk of calcium phosphate stone formation. According to a recent evaluation using US National with VA administration database it was shown that compare to the previous analysis increased in percentage of calcium oxalate (CaOx) and calcium phosphate (CaP) stones between 1996 -2003. Additionally, it was shown there was an increase percentage of a calcium phosphate stone accompanied with decrease in occurrence of calcium oxalate stone with every recurrent stone event. To date the underlying pathophysiological factors for the change in stone composition has not been fully explored. Retrospective studies have shown that increased incidence of calcium phosphate stone may occur with increased urinary pH and number of shock wave lithotripsy (SWL). In one study exploring the transformation of calcium (CaOx) to (CaP) it has been suggested that high urinary pH is intrinsic and does not occur as a consequent of renal damage following SWL.

One major challenge is that although alkali treatment is a useful countermeasure that ameliorates the risk of CaOx kidney stone formation. However, CaP saturation may increase due to an increase of urinary alkalinity negating the beneficial effects of increased citrate and decreased calcium. It has been recognized with an increase urinary pH there is an abundance of monohydrogen phosphate which increases urinary supersaturation with respect to thermodynamically instable brushite salt which converts to hydroxyapatite. However, a major physicochemical dilemma is that KCit not only increases the urinary pH but simultaneously increases urinary citrate and lowers urinary calcium.

Recently, using a new computer model JESS estimating supersaturation index by computing all pH dependent calcium citrate and calcium phosphate soluble complexes has questioned the degree of relative supersaturation ratio (RSR) has been overestimated.

The clinical studies to support or refute the above physicochemical circumstances have been very limited. In one study in patients with renal tubular acidosis with intractable calcium nephrolithiasis potassium citrate caused a significant increase in urinary pH and urinary citrate, and a decrease in urinary calcium. This treatment was associated with significant fall in RSR of calcium oxalate without a significant change in RSR brushite. During a 34 month treatment with potassium citrate treatment stone incidence significantly decrease compared to preceding 3 years before the treatment. In another long-term study treatment with potassium citrate in patients with medullary sponge kidney and nephrolithiasis treatment with KCit was also affected with significant reduction in the tone even rate commensurate with a significant rise of urinary citrate and fall in urinary calcium. In contrast in one retrospective study comparing those with transition from CaOx to CaP stones were shown urinary pH plays a key role in this transformation. Moreover, potassium citrate KCit treatment on CaP stones in a model of hypercalciuria in genetic hypercalcuric rats supported the notion that KCit may not be beneficial in preventing CaP formation.

In conclusion, it is imperative due to the above circumstances (1). To expand our knowledge, to explore pathophysiologic mechanisms of CaP stone formation (2). To utilize data registries to correlate CaP stone progression with treatment plans (3). To design prospective clinical studies comparing (a) the effects of citrate acid vs KCit (b) thiazide + KCI vs thiazide + KCit.

References:

1. Pak CY, Sakhaee K, Fuller CJ. Physiological and physiochemical correction and prevention of calcium stone formation by potassium citrate therapy. *Transactions of the Association of American Physicians*. 1983;96:294-305.

2. Mandel N, Mandel I, Fryjoff K, Rejniak T, Mandel G. Conversion of calcium oxalate to calcium phosphate with recurrent stone episodes. J Urol. Jun 2003;169(6):2026-2029.

3. Parks JH, Worcester EM, Coe FL, Evan AP, Lingeman JE. Clinical implications of abundant calcium phosphate in routinely analyzed kidney stones. *Kidney Int*. Aug 2004;66(2):777-785.

4. Parks JH, Coe FL, Evan AP, Worcester EM. Urine pH in renal calcium stone formers who do and do not increase stone phosphate content with time. *Nephrol Dial Transplant*. Jan 2009;24(1):130-136.

5. Pak CY, Moe OW, Maalouf NM, Zerwekh JE, Poindexter JR, Adams-Huet B. Comparison of semi-empirical and computer derived methods for estimating urinary saturation of brushite. *J Urol*. Mar 2009;181(3):1423-1428.

6. Pak CY, Moe OW, Maalouf NM, Zerwekh JE, Poindexter JR, Adams-Huet B. Comparison of semi-empirical and computer derived methods for estimating urinary saturation of brushite. *J Urol*. Mar 2009;181(3):1423-1428.

7. Fabris A, Lupo A, Bernich P, et al. Long-term treatment with potassium citrate and renal stones in medullary sponge kidney. *Clin J Am Soc Nephrol*. Sep 2010;5(9):1663-1668.

8. Barcelo P, Wuhl O, Servitge E, Rousaud A, Pak CY. Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. *J Urol*. Dec 1993;150(6):1761-1764.

9. Krieger Nancy, Frick Kevin, Granja Ignacio, Culbertson Christopher, Adeline Ng, Grynpas Marc, Bushinsky David. Effect of Potassium Citrate on Calcium Phosphate Stones in a Model of Hypercalciuria. *JASN*. 2015;24:1-8.

10. Sakhaee K, Alpern R, Poindexter J, Pak CY. Citraturic response to oral citric acid load. *J Urol*. Apr 1992;147(4):975-976.

When to Use Thiazides and Oral Phosphate?

Bernhard Hess
Kidney Stone Center Zurich, Klinik Im Park, Zurich, and Medical Faculty, University of Zurich, Switzerland

Thiazides

Mechanism of action

Thiazide-type diuretics (TZ) are believed to reduce calcium stone recurrence by their hypocalciuric action [1,2]. However, the clinical success of TZ therapy was not significantly associated with any changes of serum or urinary parameters [1]. Recent physiologic studies in patients with idiopathic hypercalciuria have demonstrated reduced urinary supersaturations with respect to calcium phosphate, but *not* calcium oxalate [2]. Early studies already had shown that chronic TZ treatment lowers urinary oxalate excretion, probably because TZ reduce intestinal calcium absorption, thereby leaving more calcium available for binding of oxalate in the colon [3]. This may be relevant, since from a physicochemical point of view, reducing oxaluria is more important than lowering calciuria in order to prevent calcium oxalate stone formation [4].

Clinical trials

A recent meta-analysis of 5 randomized trials (300 patients randomized) revealed moderate-strength evidence that TZ decreased the risk for stone recurrence in calcium stone formers by 48% (Risk ratio 0.52) [summarized in 5]. The drugs used in randomized trials were hydrochlorothiazide (50 mg/d), chlorthalidone (25-50 mg/d), bendroflumethiazide (2.5-5 mg/d) and the thiazide-like indapamide (2.5 mg/d). A recent retrospective study has demonstrated that chlorthalidone 25 mg/d provided a significantly greater reduction in calciuria than hydrochlorothiazide 25 mg/d [6]. However, a hydrochlorothiazide dose of 25 mg/d is considered inadaequate and not evidence-based in nephrolithiasis [7]. Nevertheless, lower TZ doses have increasingly been used for stone formers in clinical practice, probably driven by a paradigm shift toward lower TZ doses in the treatment of hypertension over the past 3 decades [7].

Adverse effects

Side-effects with adequately high TZ doses occur in 30-35% of patients [8,9]. In randomized trials, patients assigned to TZ were significantly more likely to withdraw from treatment than those assigned to placebo [5]. Potassium deficiency is quite common and may cause weakness, fatigue and – via intracellular acidosis – hypocitraturia [10]. Further metabolic side effects of TZ are hypomagnesemia, hyperuricemia/gout, reduced glucose tolerance, and zinc deficiency [8]. Additional disturbing clinical side effects are skin rashes, headaches, loss of energy and decreased libido [8].

Recommendations

Based on pathophysiologic data, TZ may be most appropriate for patients with idiopathic hypercalciuria and *calcium phosphate stones*, including those with distal renal tubular acidosis. TZ are also indicated for calcium stone formers with concomitant osteoporosis, since TZ use has been shown to reduce the risk of hip fracture by 24% [11]. If TZ are properly dosed, potassium depletion with subsequent hypocitraturia and continued stone formation may develop. This can be overcome by simultaneously administering potassium citrate [12]. Given the limited physico-chemical relevance of hypercalciuria in *calcium oxalate monohydrate stone formers*, it is debatable whether the potential reduction in oxaluria during long-term treatment outweighs the frequent side effects of properly dosed TZ.

Oral phosphate

Mechanism of action

The stone-preventive effect of orthophosphate (neutral sodium/potassium- or potassium phosphate) is thought to be due to a decrease in urinary calcium excretion and an increased inhibition of the crystallization of calcium salts in urine [13]. This probably occurs through increased intestinal binding and reduced absorption of calcium. In patients with absorptive hypercalciuria type I, neutral potassium phosphate lowered calciuria and left urinary oxalate unaltered, thereby reducing urinary calcium oxalate superaturation; brushite supersaturation remained unchanged [14].

By increasing excretion of the crystallization inhibitors citrate and pyrophosphate, calcium oxalate crystal agglomeration was also reduced [14].

Clinical trials

Several small studies [quoted in 13] had revealed evidence for the clinical efficiency of orthophosphate in calcium nephrolithiasis. However, in a carefully randomized double-blind controlled trial over almost 3 years in 71 calcium oxalate stone formers by Ettinger [15], acid potassium phosphate did not reduce stone recurrences, although urinary calcium excretion was reduced by 33%. The study was critisized for the choice of an acid instead of a neutral orthophosphate preparation, because acid phosphate lowers urinary citrate [16]. In daily doses of 1.0-1.5 g, neutral sodium-potassium-phosphate did not change the rate of stone formation over 3.1 years in 32 calcium stone formers, when the treatment period was compared with a time period of similar length immediately following the first diagnosis of stone disease, although urinary calcium excretion fell significantly and citrate tended to increase [13].

Adverse effects

Many phosphate preparations cause diarrhea and bloating. This appeared not to be the case in one study using a neutral slow-release potassium phosphate preparation [14].

Recommendations

There appears to be no sound evidence for generally recommending orthophosphate therapy [17]. Due to lack of evidence from randomized trials, the treatment is even no more mentioned in a recent comprehensive review on pharmacotherapy of nephrolithiasis [9]. Oral phosphate may be considered in highly selected cases with absorptive hypercalciuria, because it reduces intestinal calcium absorption by direct coprecipitation with calcium and decreasing circulating levels of 1,25-dihydroxyvitamin D [18].

References:

1. Ettinger B et al., J Urol 139: 679-684, 1988.

2. Bergsland KJ, Worcester EM, Coe FL. Am J Physiol 305: F592-F599, 2013.

3. Cohanim M, Yendt ER. Invest Urol 18: 170-173, 1980.

4. Robertson WG, Scurr DS, Bridge CM. J Crystal Growth 53: 182-194, 1982.

5. Fink HA et al. Ann Intern Med 158: 535-543, 2013.

6. Wolfgram DF et al. Urolithiasis 41: 315-322, 2013.

7. Vigen R, Weideman RA, Reilly RF. Int Urol Nephrol 43: 813-819, 2011.

8. Yendt ER, Cohanim M. Kidney Int 13: 397-409, 1978.

9. Moe OW, Pearle MS, Sakhaee K. Kidney Int 79: 386-392, 2011.

10. Hess B. Urolithiasis (formerly Urol Res) 34: 134-138, 2006.

11. Aung K, Htay T. Cochrane Database Syst Rev 2011 Oct 5;(10):CD005185. doi: 10.1002/14651858.CD005185.pub2.

12. Pak CYC et al. Am J Med 79: 284-288, 1985.

13. Palmqvist E, Tiselius H-G. Urol Int 43: 24-28, 1988.

14. Breslau NA et al. J Bone Mineral Res 10: 394-400, 1995.

15. Ettinger B. Am J Med 1976: 200-206, 1976.

16. Lau K et al. Kidney Int 16: 736-742, 1979.

17. Churchill DN. Mineral Electrolyte Metab 13: 243-304, 1987.

18. Insogna KL et al. J Urol 141: 269-274, 1989.

Urological treatment of stones: a moving scenario

José Manuel Reis Santos
Universidade Católica Portuguesa, Uroclínica, Centro Clínico de Urologia, Lda, British Hospital Lisbon XXI, Lisbon, Portugal

The use of anaesthetics revolutionized the treatment of bladder stones carried out by lithotomists (or barbers), since antiquity. Surgeons could begin to extract vesical stones as well as gain experience in removing renal and ureteral stones which were impossible to treat before the advent of general anaesthetics.
From the 19th century up to the 1980s all urinary tract stones were treated surgically with the aid of anaesthetics. Over the last 35 years the growing importance of minimally invasive techniques has dramatically diminished the role of open stone surgery. Since the introduction of ESWL and the endoscopic techniques, retrograde ureterorenoscopy (URS), as well percutaneous nephrolithotomy (PCNL) the open approach has been rarely used. Data from US Medicare show a decrease in open surgery from 12.5% in 1988 to 2% in 2000 (1). Other studies from European centers report similar changes from 1% to 5% (2). This is also true of other countries, for instance Pakistan, where a 26% incidence of open surgery between 1987 and 1995 decreased to 8% from 1996 to 1998 and is continually dropping today (3).
This has caused a new problem among surgeons as more than 90% of urologists aged 30 – 40 years consider themselves adequately trained in minimally invasive procedures but only 55% thought themselves trained for open surgery (4).
Current indications for open surgery are listed in the EAU and AUA guidelines and stone centers must be able to offer adequate treatment to those selected patients. It is important that the techniques of open stone removal not be completely abandoned. The decrease in classical surgical techniques for stone removal is mostly due to the introduction of ESWL in the 1980s with its rapid acceptance and technological progress. The concept of using shock waves to fragment stones was first mentioned in Russia during the 1950s. The HM-1 lithotriptor was

modified and the HM-2 appeared in 1982. This finally led to the widespread use around the world of the HM-3 in 1983.
Thousands of patients were treated in a short space of time using the Dornier HM 3. Then came the second generation lithotriptors (Siemens Lithostar) which did not need a water bath and included better imaging and ultrasound thus allowing for the treatment of children. With the Dornier HM3 most treatments were performed under general anesthesia, whereas Siemens Lithostar only required general anesthesia in 14% of the cases, including children, the rest having intravenous sedation (5). Even today extracorporeal lithotripsy is world leader in the treatment of urinary apparatus stones. However, the growth rate has stagnated due to progress in minimally invasive techniques such as PCNL, URS, RIRS and laparoscopic surgery, all of which give better stone free rates.
Percutaneous access for stone removal was first described by Fernström and Johansson (6) in 1976 since when percutaneous nephrolithotomy (PCNL) has evolved worldwide. It is now the primary approach to a large stone burden in both adult and pediatric patients (7, 8). When compared with open surgery PCNL is more cost effective, has lower morbidity and a shorter hospital stay. Complications have generally decreased and results improved. Today, in most centres, open surgery has been replaced by PCNL for the removal of large and complex stones. For complex stones PCNL can be used in conjunction with ESWL, for debulking a large stone burden as well as for ESWL failures.
Technological advances have developed new instruments such as the "mini-perc" and "ultra-mini-perc" systems that permit a choice of minimally invasive treatment for localized stones in any part of the kidney, with reduced morbidity and optimum results in both adults and children. This directly competes with advances in both rigid and flexible URS. In 1879 Thomas Emmet recorded the first surgical procedures for ureteral stones located in the distal ureter in 3 female patients. In 1889 Gustav Kolisher reported the first endoscopic stone manipulation but it was only in 1977 that Goodman developed the clinical use of rigid ureteroscopy. These early rigid ureteroscopes were of large caliber, 10 – 16 Fr, with rod lenses.

The rod lenses have now been replaced by fibro-optics and other technological advances such as cameras, intracorporeal lithotripters, ureteral access devices, stents, etc. for the post-operative phase, all of which have changed the entire field. Due to the flexible ureterorenoscopes, ureteroscopy has rapidly become the preferred treatment for ureteral stones as well as for kidney stones. Overall complication rates range from 1% - 20%, with major complications from 0% - 6%. Given all these advances ureteroscopy should be considered a first line treatment for ureteral stones, specifically where maximum efficiency and low complication rates are sought after from a single procedure. However, technological advances over the last few years have encouraged a more prudent application of minimally invasive treatment allowing for high stone-free rates associated with low morbidity, fast recovery and short hospital stay. The combination of different surgical modalities obviates the need for open surgery and amplifies the results. A combination of PCNL, retrograde intrarenal surgery for renal stones (RIRS), in conjunction with ESWL, are minimally invasive approaches for the majority of patients with more complex stones, with or without anatomical body habitus malformation, upper urinary tract or kidney deformities, morbid obesity or even bleeding disorders or other concomitant medical diseases and, last but not least, patient compliance.

In the late 1980s RIRS was used for the majority of patients to manage retained stones after failed ESWL treatment. Usually, these stone fragments were retained in the lower calyx or in the calycial diverticulum (9, 10). Today, technological refinements make RIRS a strong diagnostic tool and/or therapeutic procedure for most stone surgery and non-calculus related conditions (tumor, bleeding, strictures etc.) in the urinary tract. New tools, such as robotic endoscopic surgery and real time 3D ultrasonography, will expand and refine the results and indications and will certainly minimize complications, achieving a full stone-free result.

Recent meta-analysis shows results moving in this direction. In the near future, open surgery, or even laparoscopic surgery, robotic or not, will be the exception, only used in rare situations or concomitant surgery to other organs or pathologies.

Additional notes for the future and conclusions.

With an ever-increasing prevalence of stone disease special attention needs to be placed on:

- Primary and secondary stone prevention if we want to succeed.
- Medical community and patients must acquire effective education for lifestyle interventions.
- In case of stone in the urinary tract, Robots are potentially the next big development in URS and RIRS.
- The need for open surgery or PERC will be an exception for treatment strategies.
- The price of failure (to stop stones) will be very high even with all this technology.
- New countries or societies need to change and look for new health policies.
- As world economy has grown the prevalence of undernourishment has fallen only half as fast as poverty. Micronutrient deficiency is not falling at all. To be healthy people need not just calories but also nutrients and new life style.
- Obesity is getting worse and not only in the rich world. Between 2000 & 20013 overweight children rose from 32m to 42m, more than 2/3 of them in low and middle income countries.
- It used to be thought that when poor countries had cut hunger they would gain some respite before obesity took off. Not so!
- As under nourishement has fallen, people eating too many calories has risen, meaning that many developing countries suffer all 3 manifestation s: malnutrion- undernourishment, micronutrient deficiency and obesity, simultaineously.

If we want to achieve results similar to those for endemic bladder stones, education and full research on the understanding of the multifactorial mechanisms of stone formation will be the last goal in

avoiding stone formation in the upper urinary tract and the need for any surgery.

References:

1. Kerbl K, Rehman J, Landman J, Lee D, Sundaram C, Clayman RV. Current management of urolithiasis:progress or regress? *J. Endourol*. 2002;16:281-288.

2. Buchholz NN, Hitchings A, Albanis S. The (soon forgotten) art of open stone surgery: to train or not to train? *Ann R. Coll Surg. Engl*. 2006;88:214-217.

3. Ather MH, Paryani J, Memom A, Sulaiman MN. A 10-year experience of managing ureteric calculi: changing trends towards endourological intervention-is there a role for open surgery? *BJU Int*. 2001;88:173-177.

4. Bird VG, Fallon B, Winfield HN. Practice patterns in the treatment of large renal stones. *J. Endourol*. 2003;17:355-363.

5. Van Horn AC, Hollander JB, Kass EJ. First and second generation lithotripsy in children: Results comparison and follow-up. *J. Urol*. 1995;153:1969-1971.

6. Fernström I, Johansson B. Percutaneous pyelolithotomy. A new extraction technique. Scand *J. Urol*. Nephrol. 1976;10(3):257-259.

7. Al-Kohlany KM, Shokeir AA, Mosbah A, et al. Treatment of complete staghorn stones: a prospective randomized comparison of open surgery versus percutaneous nephrolithotomy. *J. Urol*. 2005; 173(2):469-473.

8. Shokeir AA, Sheir KZ, El-Nahas AR, et al. Treatment of renal stones in children: a comparison between percutaneous nephrolithotomy and shock wave lithotripsy. *J. Urol*. 2006; 176(2):706-710.

9. Bagley DH, Huffman JL, Lyon ES. Flexible ureteropyeloscopy: diagnosis and treatment in the upper urinary tract. *J. Urol*. 1987;138:280-285.

10. Fuchs GJ, David RD. Flexible ureteroscopy, dilation of narrow caliceal neck, and ESWL: a new , minimally invasive approach to stones in caliceal diverticula. *J. Endourol*. 1989;3:255-263.