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Clinical investigations

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The wide dissemination of extracorporeal shock-wave lithotripsy and other innovative procedures has revolutionized the surgical treatment of nephrolithiasis. The marked facility with which most stones can be removed has inevitably led to reappraisal of the need for medical diagnosis and treatment [10].

The questions that need more elaborate definition involve when, where, how and how often a patient should be evaluated. The expected rate of detection for a specific underlying physiological derangement has been reported by Coe et al. [66] to be between 80% and 90%. Recently, Pak [10] has reported similar rates regardless of whether the patient suffered from a single stone episode or from recurrent stones. However, a prospective trial by Ljunghall [8] has ably shown the futility of launching into detailed investigations after a first attack, since no additional information on the likelihood of recurrence can be gained by this approach over and above what is available on routine investigation.

In the same context, Smith [13] has commented: "When we see a patient with the first stone, usually with colic, we have no idea when the stone was made and whether he will have more. After hyperparathyroidism, gout and urinary infection have been ruled out, perhaps the single most important question is whether additional stone formation will occur in the patient, whom you follow in a continuing fashion on increased fluid intake and elimination of dietary excesses. If specific treatment is started before the metabolic activity of stone formation is known, you will never know if the treatment is necessary unless it is ineffective." This conservative approach involving fluid and diet in recurrent stone-formers has prevented new stone formation in 64%–70% of patients with a long-term follow-up, the so-called stone clinic effect [16a].

Baseline investigations of stones should always be carried out with patients maintaining their usual diet and fluid intake and continuing any necessary medication. In this way basic conditions are established that truly apply to the patient in question. As recently demonstrated by Pak [10] and by Vahlensieck and co-workers [16b] there is an enormous difference in stone-related ion excretion between ambulatory outpatients maintaining their usual diet and drinking habits and inpatients on a hospital diet (Table 1). However, one should mention that a stone is never formed under hospital conditions; therefore, it is mandatory that patients is question be investigated under conditions determined by their occupation, home and leisure time.

Thus, blood and urine samples should always be collected at equivalent times of day, so as to cut out spurious effects of food intake and biorhythms. It remains doubtful that either urine sample collected after overnight fasting or a postprandial specimen is more predictive with regard to the risk of stone formation than the customary 24 h urine collection. Unquestionably the investigation of a single urine sample can expose the influence of diet or drinking habits, but current metaphylaxis of calcium stones is based on the daily excretion of stone-forming salts.

Apart from a medical history and clinical investigation, an intravenous pyelogram (IVP) is desirable for the detection of obstruction and analysis of the stone itself; however but investigations of a patient's first stone episode may be kept within the general confines of what is possible in any general practice. The investigations

Table 1. Urinary parameters measured over 24 h in recurrent calcium stone-formers on normal vs hospital diets

mmol/l	Outpatient, normal diet	Inpatient, hospital diet
Calcium	5.03 +/− 2.15	3.80 +/− 1.60
Oxalate	0.35 +/− 0.20	0.36 +/− 0.18
Uric acid	3.03 +/− 0.37	2.66 +/− 0.51
Citric acid	2.56 +/− 1.42	3.12 +/− 1.01
Sodium	174.5 +/− 52.3	121.8 +/− 30.9
Magnesium	4.97 +/− 1.7	4.3 +/− 1.3
Creatinine	19.3 +/− 7.1	14.3 +/− 4.1

Vahlensieck et al. [16b]

Table 2. Laboratory investigations that should be carried out in patients experiencing their first stone episode

Serum parameters:	Calcium Creatinine Sodium Potassium Uric acid
Fresh voided urine:	pH Specific gravity Protein Red cells Leucocytes Bacteria crystals

Table 3. Laboratory investigations of serum parameters that should be performed in recurrent calcium stone-formers

Serum parameters:	Calcium Creatinine Sodium Potassium Uric acid Chloride (Parathormone) (Magnesium) (Inorganic phosphate)

Table 4. Laboratory investigations of urinary parameters that should be carried out in recurrent calcium stone-formers

Fresh voided urine:	No additional investigations over first stone episode	
24-hour-urine-sample:	Calcium Oxalate Uric acid Creatinine Citric acid Magnesium Phosphate	basic screen
Advanced tests:	Chloride Potassium Sodium (Ammonium) (Sulfate)	

comprising any basic screening panel in patients experiencing their first stone episode are shown in Table 2. In cases showing hypercalcemia on routine analysis or repeated high serum calcium values while fasting, screening for hyperparathyroidism should be done, for example evaluation of serum parathormone and measurement of bone density. All patients with signs of a urinary tract infection (UTI) should undergo a bacteriological examination.

If a patient presents with recurrent calcium-containing stones, a full diagnostic search is mandatory (Tables 3 and 4). Attainment of the full diagnostic value requires that the stone-risk profile be interpreted within the context of clinical and nutritional history and other available laboratory data. An intravenous pyelogram (IVP) with stone analysis is advisable.

Table 5. Laboratory methods commonly used in calcium urolithiasis

Calcium	Atomic absorption spectroscopy (Flame photometry)
Oxalate	Enzymatic oxidase method Gas chromatography HPLC
Uric acid	Uricase reaction and ultraviolet absorption spectrophotometry
Sodium	Flame photometry Ion selective electrode
Potassium	Flame photometry Ion selective electrode
Ionized calcium	Ion-selective electrode
Parathormone	Radioimmunoassay
Phosphate	Phosphomolybdate reaction
Citric acid	HPLC
Chloride	Ion-selective electrode
Magnesium	Atomic absorption
Ammonium	Ion-selective electrode

The presence of abnormal environmental risk factors could indicate nutritional aberrations. Thus, a low urine output may reflect decreased fluid intake or excessive extrarenal fluid loss; high urinary sodium, exaggerated salt intake; increased urinary phosphate and sulfate, abnormally high consumption of animal proteins; and decreased urinary magnesium, deficient magnesium intake. These dietary aberrations may contribute to or cause abnormalities in certain metabolic risk factors. For example, a high sodium intake augments calcium excretion, and excessive consumption of animal proteins may increase urinary calcium and uric acid and reduce urinary citrate and pH. High urinary oxalate would suggest enteric hyperoxaluria in patients with ileal disease, or dietary hyperoxaluria if there is excessive ingestion of oxalate-rich foods, for example rhubarb, spinach, peanuts, cacao, chocolate or a vitamin C substrate.

A list of more advanced studies designed to supplement the basic screen is given in Tables 3 and 4. In most cases this advanced panel of investigations cannot be carried out in a general practice setting without the help of larger laboratories. The laboratory methods most commonly used are shown in Table 5. Because most of these tests are in widespread use, I would not like to go into the particulars; this should be done, if necessary, in the roundtable discussion. Instead I shall discuss some points concerning the last slide.

The increasing use and extended indications of the sodium/potassium citrate formulation directs our interest to hypocitraturia (Table 4). Hypocitraturia often results from acidosis secondary to a variety of disturbances, including distal renal tubular acidosis, acquired acidosis of

Table 6. Advanced laboratory investigations performed in recurrent calcium stone-formers

Differentiation of hypercalciurias
Screening for distal renal tubular acidosis
Quantitative estimation of crystalluria (Coulter counter)
Low-molecular-weight inhibitors
Oral loading tests (purine, oxalate)
Measurement of crystallisation conditions in urine
Measurement of crystal growth and aggregation
Computerized calculation of supersaturation (EQUIL II)
Computerized calculation of stone forming risk
Search for high-molecular-weight inhibitor proteins (gel electrophoresis)

Table 7. Protocol used to differentiate among the 3 types of hypercalciuria

1. Low-calcium diet for 3 full days prior to test period (restricted milk and dairy produce)
2. Day 1 No food as of 8 p.m. except 1.5 l distilled water or mineral water low in calcium content
3. Day 2 Accurate collection from 6 to 10 a.m. (starved patients) of 4-h urine for laboratory estimation of calcium, creatinine (if possible plus c-AMP)
10 a.m.: blood sample for calcium, creatinine (if necessary, ionized calcium, parathormone) estimation
a.m.: 1 g calcium by mouth (e.g. 2 tabs. Calcium Sandoz forte à 500 mg)
10 a.m. – 2 p.m.: urine collection for laboratory analysis of calcium, creatinine (if possible, c-AMP)

chronic diarrheal states, lactic acidosis from physical exercise, consumption of a diet rich in acid content and potassium loss due to thiazide therapy or a high-sodium intake, resulting in intracellular acidosis. Hypocitraturia is also encountered in patients with active UTI.

If one suspects the enteric type of secondary hyperoxaluria, a so-called oral oxalate-loading test can be performed. This test, originally described by Rampton et al. [11], measures urinary oxalate after an oral load of 600 mg sodium oxalate, supplied in gelatine capsules containing each 300 mg. More interestingly, some intestinal disorders cause steatorrhoea, for example Crohn's disease, jejunoileal bypass for morbid obesity, coeliac disease and pancreatitis. Thus, the ingested calcium is bound to fatty acids and the remaining oxalate can be absorbed. Usually 90%–98% of the ingested oxalate is bound to calcium and excreted with the faeces. However, these are relatively rare causes of secondary hyperoxaluria; the uppermost cause is a low-calcium diet, in most cases prescribed by the responsible physician, which results in increased intestinal oxalate absorption.

Further studies, for example screening and differentiation of hypercalciuria, screening for distal renal tubular acidosis, purine- or oxalate-loading tests, searches for low complexing or high-molecular-weight inhibitors and precipitation studies, should be reserved for patients with frequent stone recurrences and should only be done by an experienced stone clinic or in research programs (Table 6). Table 6 summarise the far advanced tests that should be done if one of the above-mentioned disorders is suspected.

Hypercalciuria

A number of investigations, originally described by Pak et al. [10a] and Nordin et al. [9a] and modified by numerous institutions, are cited as being capable of distinguishing among the three types of hypercalciuria (Table 7). However much they may differ in detail, all of these procedures have in common the measurement of calcium excretion following a period of starvation and a subsequent oral calcium load. Patients with recurrent calcium stones who have on one occasion been demonstrated to be hypercalciuric are required to adhere to a low-calcium diet for a period of 3 days before commencing the test. At the end of this period they are starved for a minimum of 12 h, during which adequate diuresis is secured. At the end of the starvation period urine is collected over an interval of 2–4 h.

Oral calcium loading can now be performed by the administration of a 1 g bolus. This is followed by a defined period of urine collection. Urinary calcium, creatinine and, if possible, cyclic AMP values are estimated. The calcium:creatinine ratio is estimated for the samples from starved patients and those collected after calcium loading [9] (Table 8). In the presence of absorptive hypercalciuria, both calcium excretion and the urinary calcium:creatinine ratio increase after an oral calcium load, the starving values having been normal. In both renal and resorptive hypercalciuria, raised calcium excretion and a correspondingly increased calcium:creatinine ration occur under both starved and calcium-loaded conditions. Oral calcium loading leads to only a small increase.

The measurement of urinary cyclic AMP helps to differentiate between renal and resorptive hypercalciuria in that urinary excretion is raised under conditions of starvation in renal hypercalciuria. For metaphylaxis of calcium stones it is important that absorptive hypercalciuria be detected and differentiated from the other types. The former is successfully treated by a low-calcium diet; the other types can be corrected by the use of thiazides, whereas in absorptive hypercalciuria thiazides cause only a transient decrease in urinary calcium excretion.

Distal renal tubular acidosis

Common laboratory findings in distal renal tubular acidosis are hyperchloremia, hypopotassemia and, in the proven absence of urease-positive bacterial infection, a urinary pH that is consistently above 5.8 (Table 9). In patients with these findings and hypercalciuria, renal tubular acidosis must be strongly suggested. In these cases an ammonium chloride test according to Wrong and Davies [18] should be done. Diagnosis can be established be measuring the urinary pH after an oral load of 0.1 mg/

Table 8. Urinary parameters determined in recurrent calcium stone-formers demonstrating hypercalciuria

	Urinary calcium: creatinine ratio		cAMP: creatinine	
	Starved period	Calcium loaded (oral)	Starved period	Calcium loaded (oral)
Resorptive (hyperparathyroidism)	Raised	Raised	Raised	Raised
Renal	Raised	Raised	Raised	Normal
Absorptive/intestinal	Normal	Raised	Normal	Normal

Table 9. Laboratory screening for distal renal tubular acidosis according to Wrong and Davies [18]

Ammonium chloride tolerance test [14]
Urine pH consistently > 5.8 Absence of urease-positive UTI
Oral load with 0.1 g/kg body weight ammonium chloride in gelatine capsules
Urine pH < 5.4: RTA excluded
Urine pH > 5.4: Blood gas analysis Low bicarbonate: Complete RTA High bicarbonate: Incomplete RTA

Test according to Wrong and Davies [18]

Table 10. Laboratory investigations for determination of crystallisation conditions in urine

Direct measurement of inhibitor capacity [3]
Quantitative determination of inhibitors of calcium phosphate in whole urine [4]
Oxalate tolerance method [9]
Gel crystallisation method [1]
Rapid evaporation technique [7]
Seeded crystal growth method for measuring the effects of compounds or urine on the solubility, the growth and the agglomeration of calcium oxalate monohydrate crystals [17]
Method for determination of the risk of calcium oxalate crystallisation in urine [16]

kg ammonium chloride. A mild acidosis detected by blood-gas analysis and a urinary pH that is at no time lower than 5.4 confirm the diagnosis.

Computer programmes for calculation of urinary supersaturation

Dedicated computer programmes developed by Finlayson and Reid [6a] are in widespread use to calculate the saturation level of total sodium, potassium, ammonium, calcium, magnesium, phosphate, sulfate, oxalate, citrate, urate and chloride as well as the volume and pH of the urine (Table 6). Strikingly, a 1% increase in oxalate concentration did more to raise saturation than did calcium; furthermore, the inhibitory effect of citrate on calcium oxalate precipitation ranked higher than those of sodium, phosphate, magnesium, sulfate, potassium and chloride together. One drawback is that macromolecular inhibitors are not taken into account.

These programmes and others developed by Robertson et al. [12] or Tiselius [15] for calculation of the stone-forming risk may help to identify a patient at risk of forming stones and to decide on an appropriate therapy. However, one should bear in mind that these calculations and all of the above-mentioned investigations are based on either a 24-h specimen or a single urine sample, which in no case represents the conditions under which a given stone is formed.

Systems for measuring crystallisation conditions in urine

Systems measuring nucleation and growth in initially crystall-free urine give an estimate of the general risk of crystallisation, which in the studies of Briellmann et al. [5] and Tiselius [16] was not significantly higher in urine of stone-formers than in that of healthy controls (Table 10). In general these methods are suitable for evaluation as to whether metaphylaxis is necessary and, if so, for the follow-up of individual stone therapy.

One problem arising from the comparison of urinary inhibitor measurements from different centers is that each group of workers tends to use a different method for assessing "inhibitory activity" in urine and in urine preparations, for example whole urine, diluted urine or evaporated urine. Another problem is that there is no consensus, in the literature or at meetings about the definition of "inhibitory activity" or of "inhibitors of crystallisation". A further problem in defining an inhibitor is the decision as to whether it acts as a complexor of calcium oxalate or phosphate or whether it functions primarily as a crystal poison at concentrations below those at which significant complexation occurs [2].

The last important problem is how to treat and store urine between the time of voiding and the measurement of inhibitory activity. Generally, each center does and can use its established test system to control and to decide when to start a given stone therapy.

To answer the questions posed at the beginning of this paper concerning the timing and intensity of the evaluation in a given patient with recurrent calcium stones, I

Table 11. Indications for laboratory screening in recurrent calcium stone-formers

Hypercalciuria differentiate	absortive renal resorptive (HPT?)
Hyperoxaluria oral oxalate load	enteric type? intestinal disorder
Urine pH > 5.8 screen for	Distal renal acidosis (RTA) UTI
Serum calcium > 2.65 mmol/l with hypercalciuria	Hyperparathyroidism RTA milk-alkali syndrome Vitamin D intoxication
Urine pH < 5.5 screen for	Hyperuricuria
No metabolic disorder screen for	Hypocitruria Inhibitors

would like to emphasize the following points (Table 11). In cases of hypercalciuria, one should differentiate between the absorptive disorder and the other types. In hyperoxaluria, one should exclude intestinal disorders and look for enteric causes, such as dietary excesses. Patients with urinary pH that is consistently above 5.8 should be screened for distal renal tubular acidosis. UTI must be excluded. Serum calcium levels above 2.65 are suspicious of primary HPT, but other diseases should be considered. Urine pH consistently lower than 5.5 is often found in hyperuricuric states. In these cases one should search for gouty disease.

Following these suggestions, one can usually detect a metabolic disorder in about 24% of patients [10]. Regardless of low urinary outputs, urinary pH derangements, infection or dietary excesses, a high percentage of recurrent stone-formers remain that have so-called idiopathic stone disease.

One question remains: How often should a patient with recurrent calcium stones be investigated? In my opinion (but this is open for discussion) one control per year should be sufficient, but the timing must be accommodated to the metabolic activity of the stone disease, i.e. a malignant type requires earlier and more intensiver controls.

In summary we should use modified diagnostic screening that is adapted to the patient in question. A basic screen is applicable for a patient's first stone episode and should be feasible in any general practice. More sophisticated investigations are necessary in a patient with recurrent calcium stone disease. However, any metabolic disorder detected on routine screening should be investigated in a so-called stone clinic or by institutions acquainted with screening for calcium stone disorders.

References

1. Achilles W (1985) The gel crystallisation method. Fortschr Urol Nephrol 23:252
2. Baumann JM (1988) How to measure crystallisation conditions in urine: a comparison of 7 methods. Urol Res 16:137
3. Bauman JM, Lauber K, Lustenberger FX, Wacker M, Zingg EJ (1985) The direct measurement of inhibitory capacity in urine. Urol Res 13:169
4. Bisaz S, Felix R, Neumann WF, Fleisch H (1978) Quantitative determination of calcium-phosphate precipitation in whole urine. Miner Electrolyte Metab 1:74
5. Briellmann Th, Seiler H, Hering F, Rutishauser G (1985) The oxalate tolerance method. Urol Res 13:291
6. Coe FL, Keck J, Norton ER (1977) The natural history of calcium urolithiasis. JAMA 238:1519

6a. Finlayson B, Reid (1978) The expectation of free and fixed particles in urinary stone disease. Invest Urol 15:442

7. Hallson PC, Rose GA (1978) Rapid evaporation technique. Br J Urol 50:442
8. Ljunghall S (1978) Incidence and natural history of renal stone disease and its relationship to calcium metabolism. Eur Urol 4:424
9. Lutzeyer W, Hering F (1986) Drug therapy of urinary calculi and prevention of recurrence. In: Schneider SJ (ed) Urolithiasis: therapy and prevention. Springer, Berlin Heidelberg New York, p 1

9a. Nordin BEC (1976) Calcium, phosphate and magnesium metabolism. Clinical physiology and diagnostic procedures. Churchill Livingstone, Edinburgh London New York

10. Pak CYC (1988) Medical management of nephrolithiasis in Dallas: update 1987. J Urol 140:461

10a. Pak CYC et al. (1974) The hypercalciurias. Causes, parathyroid function and diagnostic criteria. J Clin Invest 54:382

11. Rampton DS, Kassidas GP, Rose GA, Sarner M (1979) The oxalate loading test – a screening for steatorrhoea. In: Rose GA, Robertson WG, Watts RWE (eds) Oxalate in human biochemistry and clinical pathology. Wellcome Foundation, London, pp 264
12. Robertson WG, Peacock M, Nordin BEC (1968) Activity products in stone-forming and non-stone-forming urine. Clin Sci 34:579
13. Smith LH (1982) Editorial comment. J Urol 127:858
14. Sommerkamp H (1977) Diagnostik der renalen tubulären Azidose. Fortschr Urol Nephrol 9:165
15. Tiselius HG (1983) Different estimates of the risk of calcium oxalate crystallisation in urine. Eur Urol 9:231
16. Tiselius HG (1985) A method for determination of the risk of calcium oxalate crystallisation in urine. Urol Res 13:297

16a. Vahlensieck (1986) Diagnosis of urinary calculi. In: Scheider HJ (ed) Urolithiasis. Springer, Berlin Heidelberg New York

16b. Vahlensieck et al. (1985) Metabolic investigations in 407 recurrent stone formers and healthy controls on condition of individual as well as standard diet. In: Smith LH, Robertson WG, Finlayson B (eds) Urolithiasis. Plenum, New York London, p 29

17. Will EJ, Bijvoet OLM, Blomen LJMJ, Van der Linden H (1983) A seeded crystal growth method for measuring the effects of compounds or urine on the solubility, the growth and the agglomeration of calcium oxalate monohydrate crystals. J Cryst Growth 64:297
18. Wrong O, Davies HEF (1959) The excretion of acid in renal disease. R J Med 28:259

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