

Metabolic Evaluation and Medical Management of Upper Urinary Tract Stone Disease

Guidelines from the Scandinavian Cooperative Group for Urinary Stones

Palle Jörn Osther,¹ Lars Grenabo,² Gudjon Haraldsson,³ Göran Holmberg,⁴ Ossi Lindell,⁵ Peter Mogensen,⁶ Alexander Schultz,⁷ and Nils Magnus Ulvik⁸

From the Departments of Urology, ¹Odense University Hospital, Odense and ⁶Copenhagen Stone Center, Frederiksberg Hospital, University of Copenhagen, Copenhagen, Denmark, ²Sahlgrenska University Hospital, Göteborg and ⁴Umeå University Hospital, Umeå, Sweden, ³Lanspítalinn, Reykjavík, Iceland, ⁵Meilahti Hospital, University of Helsinki, Helsinki, Finland, ⁷The National Hospital, University of Oslo, Oslo and ⁸Haukeland Hospital, University of Bergen, Bergen, Norway

(Submitted April 16, 1999. Accepted for publication April 29, 1999)

Scand J Urol Nephrol 33: 372–381, 1999

A set of simple guidelines for metabolic evaluation and medical/dietary management of patients with urolithiasis is presented. The evaluation scheme is based on the documented risk factors in the Nordic area and the results of controlled clinical trials, and takes its basis in the severity of the stone disease in the individual stone patient. The initial evaluation in all patients aims at diagnosing conditions with a definitive metabolic, infectious or anatomical/functional cause of stone formation (MIAF urolithiasis). Patients with MIAF urolithiasis are treated according to the nature of the underlying disease. Having excluded/diagnosed MIAF urolithiasis, patients with idiopathic calcium nephrolithiasis remain, and in this group, which comprises approximately 85% of the total stone population in the Scandinavian region, only those with a complicated stone disease are subjected to additional evaluation, which aims at identifying underlying pathophysiological derangements for which medical therapy has been proven to be effective in controlled clinical trials.

Key words: kidney calculi, medical treatment, metabolic evaluation.

Palle J. Osther, MD, PhD, Department of Urology, Odense University Hospital, DK-5000 Odense C, Denmark. Tel: +45 65412203. Fax: +45 66153257. E-mail: palle.osther@dadlnet.dk

Urinary stone disease can be divided into two groups: conditions with a definitive metabolic, infectious or anatomical/functional cause of stone formation (MIAF urolithiasis) (Table I); and idiopathic urolithiasis. The principles of investigation and management of MIAF urolithiasis are generally accepted and uniform worldwide. However, with regard to metabolic evaluation and medical/dietary management of idiopathic urolithiasis, the principles of action differ widely from centre to centre even within the same country and clinical treatment is often based on “what has always been done”. This is due to the multifactorial nature of the disease, which has a large number of possible risk factors that have often been arbitrarily defined many years previously in populations that differ markedly from our own population, and, furthermore, the lack of fully controlled trials, both with regard to drug treatment and dietary intervention (1). This understandably leaves many clinicians reluctant to introduce extensive evaluation and treatment programs.

These considerations have led the Scandinavian Cooperative Group for Urinary Stones to propose guidelines for metabolic evaluation and dietary and medical management of urolithiasis, based on the documented relevant risk factors in the Nordic area and the results of controlled clinical trials.

PURPOSE OF EVALUATION

The metabolic evaluation of stone patients has two objectives: (i) diagnosis of conditions with MIAF urolithiasis; and (ii) diagnosis of treatable derangements in idiopathic calcium nephrolithiasis.

MIAF urolithiasis

Urolithiasis may be a complication of several “primary” disorders. These conditions are characterized by overt metabolic or other derangements, which, if not diagnosed and specifically treated, will result in recurrent stone formation and potential loss of renal

Table I. Conditions with a definitive metabolic, infectious or anatomical/functional cause of stone formation (MIAF-urolithiasis)

Defects in purine metabolism (uric acid related disorders)
Hyperoxaluric states
Primary hyperoxaluria
Enteric hyperoxaluria
Hypercalcaemic states
Primary hyperparathyroidism
Hyperthyroidism
Vitamin D abuse
Immobilization
Disseminated malignancies
Sarcoidosis
Renal tubular acidosis
Chronic diarrhoeal states
Cystinuria
Urinary infection with urease producing microorganisms
Anatomical and functional abnormalities

function and/or failure of other organ systems (Table I). Although these conditions only comprise about 10–15% of all cases of urolithiasis in the Nordic area, MIAF urolithiasis should be ruled out in all patients presenting with urinary tract stone disease, since most of the patients will need some form of prophylactic intervention. A basic evaluation program for all patients with urolithiasis should therefore be designed to diagnose such cases.

Idiopathic urolithiasis

The majority of stones formed in the kidney contain calcium as a main component (calcium nephrolithiasis). This type of stone formation is usually idiopathic, in the sense that the patients are without overt metabolic, infectious or anatomical/functional (MIAF) disease (Table I). However, a wide variety of metabolic derangements that may contribute to stone formation have been described in patients with idiopathic nephrolithiasis, including urinary solute excess and crystal modifier defects, as well as factors involved in crystal retention in the renal tubules. The exact role of these conditions and their possible interrelationship remain matters of debate, and, furthermore, at present only a few of these can be modified effectively in the direction of reducing stone recurrence.

Epidemiological and metabolic studies have implicated the intake of a number of nutrients in the aetiology of renal stones, including low fluid intake, dietary excess of animal proteins, oxalate and sodium and a high/low intake of calcium, as well as several other nutritional factors (2, 3). Over the years, stone patients have been overwhelmed by a staggering number of dietary recommendations. Few of these have been documented as effective in preventing recurrence. Since dietary recommendations will have life-long implications for the patients, the completion of controlled studies or collection of epidemiological

Table II. Classification of stone patients according to severity of stone disease

Simple stone disease
Single stone former with spontaneous passage of stone
Unilateral typical radiopaque stone that is easily fragmented and cleared from the renal tract following ESWL (Extracorporeal Shock Wave Lithotripsy) and/or endoscopic surgery
Insignificant* recurrence of typical radiopaque stone
Complicated stone disease
Suspicion of MIAF-urolithiasis
Significant recurrence#
High stone burden†
Early stone debut (<20 years)

MIAF-urolithiasis = conditions with a definitive metabolic, infectious or anatomical/functional cause of stone formation

*A recurrent stone that does not significantly affect the life of the patient, for instance spontaneous passage of a stone 6 years after the previous stone.

#Significant recurrence refers to a recurrent stone(s) that significantly affect the life of the patient, for instance recurrence of a 2-cm kidney stone within 5 years of the previous stone. The terms "significant" and "insignificant" recurrence give the possibility for physicians to use their individual judgement, since a recurrent stone in one patient will not be identical to a recurrent stone in another patient.

† Particularly large stones (>2 cm) and/or extensive bilateral stone disease.

data should be mandatory before significant dietary modifications can be justified.

PRACTICAL EVALUATION

Controversy exists with regard to the extent of evaluation in patients with idiopathic urolithiasis. The evaluation scheme presented below has been designed using the following principles:

1. Extended evaluation (i.e. evaluation beyond exclusion/diagnosis of MIAF urolithiasis) should be performed only in cases in which both patient and physician are willing to accept the consequences of the possible findings of such an evaluation. Thus, the patients need to be prepared to undergo medical therapy and/or dietary modifications. Furthermore, the effect of the medical and/or dietary treatment options need to be well-documented, otherwise, life-long medical and/or dietary intervention cannot be justified. The patient's motivation for life-long prophylaxis depends on how seriously the stone disease affects his or her life. Based on these assumptions, stone disease in any individual may be classified as either "simple" or "complicated". The concept of these two entities are defined in Table II, and it is assumed that patients with a complicated stone disease are candidates for prophylactic intervention, whereas patients with

a simple stone disease are not, unless evaluation unveils an obvious underlying abnormality (MIAF urolithiasis) that makes treatment mandatory.

2. For a condition to be considered a risk factor, its possible role in stone formation should be justified in pathophysiological terms and it should be altered significantly in stone patients compared with a contemporary cohort of control subjects, otherwise the limits of normal cannot be defined in the stone patient population. The use of "normal limits" defined in populations that differ markedly from one's own is not acceptable.
3. In clinical practice it can only be justified to examine for "treatable" risk factors. These are risk factors in which correcting the abnormality will result in a significantly lower recurrence rate, as documented in fully controlled clinical trials.

On the basis of these principles, the following two-step evaluation scheme ("basic" and "extended" metabolic evaluation) is suggested (Fig. 1).

Basic metabolic evaluation

Basic metabolic evaluation should be performed in all patients with stone disease; this will lead to diagnosis of the most important causes of MIAF urolithiasis. The following scheme is employed for basic evaluation:

1. Medical history for any underlying conditions (bowel disease, bone disease, etc.) that may have contributed to stone formation, family history, dietary habits and medication.
2. Plain abdominal X-ray and intravenous pyelograms and/or ultrasonographic examinations should be available to unveil anatomical abnormalities, identify nephrocalcinosis, plan additional lithotripsy/endoscopic procedures and assess stone burden.
3. Spot urine sample is collected for culture and pH.
4. Stone material (if available) is analysed to determine the crystalline composition.
5. Blood sample is taken for measurement of plasma concentrations of creatinine, urate and calcium.

The basic metabolic evaluation may require additional examinations in selective cases in order to establish the exact diagnosis. For further information see the section below on selective medical management of MIAF-urolithiasis.

In performing the basic metabolic evaluation and additional tests derived from this, conditions with MIAF urolithiasis should be excluded/diagnosed. This will leave about 80–85% of the stone population without a definite pathophysiological diagnosis. Pa-

tients with a simple stone disease and no evidence of MIAF disease ("uncomplicated idiopathic calcium nephrolithiasis") need no further examination, since prophylactic intervention can hardly be justified in these patients. The remaining group with complicated urolithiasis and no evidence of MIAF disease ("complicated idiopathic calcium nephrolithiasis") should, however, undergo an additional evaluation, directed at the identification of underlying pathophysiological derangements in which medical therapy have been proven effective in controlled clinical trials. These considerations lead to the suggestions for further evaluation in "complicated" idiopathic calcium nephrolithiasis described below.

Extended metabolic evaluation

Extended metabolic evaluation is the second step in the evaluation of patients with complicated urolithiasis and no definite diagnosis at basic metabolic evaluation. It consists of a 24-h urine sample analysed for volume, creatinine, calcium and citrate.

Creatinine is included in order to validate a complete 24-h sample period. Volume, calcium and citrate measurements meet the principles of evaluation mentioned above (see next sections). (This is not the case for urinary magnesium, urate and oxalate. In the Nordic area there seem to be no significant differences between idiopathic stone formers and healthy subjects with regard to these quantities, thus routine determination of urinary magnesium, urate and oxalate in idiopathic stone formers cannot be justified (4–8).)

It should be emphasized that the above-mentioned evaluation program is considered the minimum evaluation. Stone centres with selected stone populations may need a more comprehensive evaluation scheme. This is also the case, if estimates of urinary supersaturation of different stone salts are used to monitor the effect of intervention. The superiority of using such indices has not, however, been demonstrated in controlled trials.

SELECTIVE MEDICAL MANAGEMENT OF UROLITHIASIS

The rationale for selective medical management of urolithiasis is based on the assumption that particular pathophysiological alterations are directly involved in the formation of renal stones and that the identification and correction of these alterations will prevent stone formation (9). This is confirmed by controlled clinical trials, which have shown that selective medical therapy is more effective and safer in preventing recurrence than "random" treatment. The following treatment program is based on the principle of selective treatment (Table III).

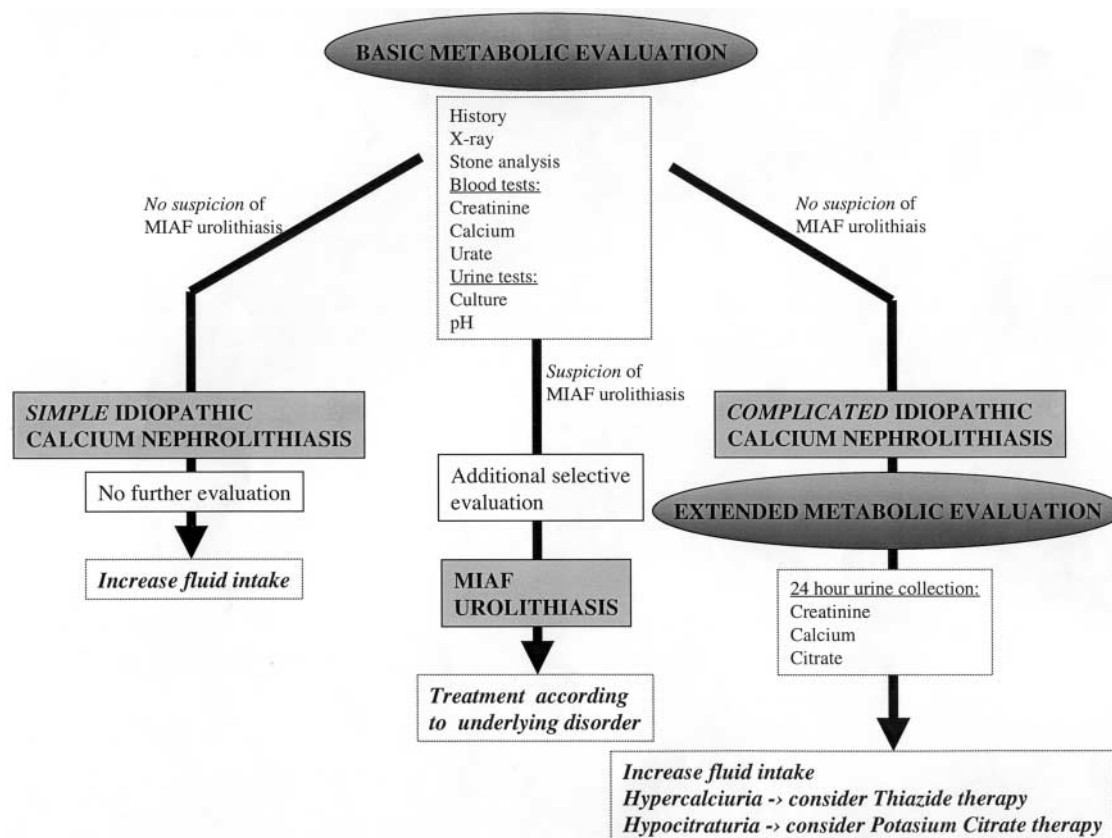


Fig. 1. Flow-chart for evaluation and medical management of patients with upper urinary tract stone disease. MIAF-urolithiasis: conditions with a definitive metabolic, infectious or anatomical/functional cause of stone formation. Additional selective evaluation for diagnosis of MIAF urolithiasis may, for instance, be 24-h urine analysis of oxalate in patients with bowel disease, and, in calcium urolithiasis presenting in childhood, for diagnosis of enteric hyperoxaluria and primary hyperoxaluria; plasma parathyroid hormone in cases of raised levels of plasma ionized calcium for diagnosis of primary hyperparathyroidism; systemic acid-base status and 24-h urinary citrate and calcium excretion in cases of nephrocalcinosis or extensive bilateral calcium urolithiasis for diagnosis of distal RTA (renal tubular acidosis); urinary cystine analysis in cases of weak radiopaque stones; and urinary calcium and citrate excretion in cases of medullary sponge kidney; or additional tests dictated by the outcome of stone analysis. For further details, see the section on MIAF urolithiasis in the text.

MIAF UROLITHIASIS

Defects in purine metabolism

Uric acid nephrolithiasis. Uric acid stones are radiolucent. The major goal in the management of recurrent uric acid nephrolithiasis is to increase the urinary pH to above 5.5 (preferably to approximately 6.5–7.0) in order to reduce the concentration of undissociated uric acid. This may be done by any form of alkali therapy. Sodium alkali (i.e. sodium bicarbonate) treatment may result in an increase in renal calcium excretion, thereby increasing the risk of calcium phosphate stone formation in an alkaline urine (10). Potassium alkali (i.e. potassium citrate), therefore, seems to be more appropriate (11). If hyperuricaemia (gout) is present, allopurinol is recommended.

Hereditary xanthinuria and 2,8-dihydroxyadeninuria. Hereditary xanthinuria and 2,8-dihydroxyadeninuria are rare causes of radiolucent stones, which

may be confused with uric acid calculi. Furthermore, patients who are given allopurinol for uric acid nephrolithiasis may occasionally develop xanthine calculi because allopurinol blocks the conversion of xanthine to uric acid. Treatment of a xanthine calculus consists of increased fluid intake. 2,8-dihydroxyadenine calculi may be treated by a low-purine diet and allopurinol.

Hyperoxaluric states

Primary hyperoxaluria type 1. Primary hyperoxaluria type 1 is a rare autosomal recessive disorder, which should always be suspected in children presenting with renal calcareous stones or nephrocalcinosis. Diagnosis is strongly suspected when renal oxalate excretion rate is $>1 \text{ mmol}/1.73 \text{ m}^2/24 \text{ h}$ (urinary glyoxylate and glycolic acid are also raised). Diagnosis is confirmed by liver biopsy measuring alanine: glyoxylate aminotransferase activity and/or DNA-

analysis. Genetic counselling is recommended in order to calculate the risk for future pregnancies. Prenatal diagnosis is possible. As the nephrocalcinosis progresses a high percentage of the children will develop renal failure. Treatment with a combination of high fluid intake (>2 l/m²), pyridoxine (300–600 mg/m²) and alkaline citrate (0.15 g/kg) have recently proved promising in stabilizing/improving renal function and reducing stone passage (12). With increasing loss of renal function, systemic oxalosis may develop. No form of dialysis is able to remove sufficient quantities of oxalate, and combined liver and kidney transplantation is the treatment of choice in cases with end stage renal disease. If transplantation is performed before severe oxalosis is present, the results are good. Preliminary data suggest that citrate therapy should be continued after transplantation in order to reduce calcium oxalate depositions in the transplanted kidney due to gradual resolubilization of calcium oxalate deposited throughout the body (12).

Primary hyperoxaluria type 2. Primary hyperoxaluria type 2 is caused by deficiency of D-glycerate dehydrogenase in liver, white blood cells and other tissues. Recurrent urolithiasis may occur. Only a few cases have been reported to progress to end stage renal disease.

Diagnosis, treatment and follow-up of primary hyperoxaluria should preferably be performed in collaboration with the paediatrician/nephrologist.

Enteric hyperoxaluria. Enteric hyperoxaluria should be suspected in stone patients with malabsorption syndromes with steatorrhoea (i.e. chronic inflammatory bowel disease and patients who have undergone small bowel resection). Stone disease usually results from high urinary oxalate excretion (>0.5 mmol/24 h) and low urinary volume (13). Additionally, hypocitraturia may be present due to moderate extracellular non-carbonic acidosis (intestinal base loss). Dietary evaluation by a dietician is advisable. A high fluid intake and avoidance of oxalate- and fat-rich foodstuffs are recommended. Alkaline citrate therapy may be indicated in the presence of non-carbonic acidosis (hypocitraturia). This treatment will protect against stone formation as well as bone dissolution. Theoretically, calcium citrate should be the treatment of choice, acting by binding oxalate in the intestinal tract (calcium), and by correcting systemic acid-base disturbances (citrate). However, no clinical data are available on this treatment modality.

Thus, unlike idiopathic urolithiasis, urinary oxalate measurements should be performed routinely in cases of urolithiasis presenting within the first two decades of life and, in cases of nephrocalcinosis for diagnosis of

primary hyperoxaluria and for diagnosis of enteric hyperoxaluria in cases of bowel disease.

Hypercalcaemic states

Primary hyperparathyroidism. Primary hyperparathyroidism is diagnosed by increased levels of serum calcium and, subsequently, increased levels of serum parathyroid hormone. The optimum treatment is parathyroidectomy. Recurrent nephrolithiasis after surgery demands an extended metabolic evaluation.

Other hypercalcaemic states. Other hypercalcaemic states are treated according to the underlying disease. Often treatment cannot be curative, but is directed only at a symptomatic correction of the hypercalcaemia.

Renal tubular acidosis

Nephrolithiasis is a problem in only type 1 (distal) renal tubular acidosis (RTA). Patients are characterized by hyperchloraemic hypokalaemic non-carbonic acidosis. The rare classic hereditary form presents in early childhood. Acquired forms and an incomplete form without overt systemic acidosis also exist (14). The massive recurrent stone formation (usually calcium phosphate) and nephrocalcinosis are due to a combination of hypercalciuria, hypocitraturia and a paradoxically high urine pH. Treatment aims at correcting the acidosis. Potassium citrate is the preferred treatment. This treatment will correct the acidosis and the hypokalaemia and has been shown to reduce stone frequency (as well as improving/stabilizing kidney function and protecting bone) significantly by decreasing urinary calcium excretion and increasing citrate excretion (15). Sodium alkalis are less suitable due to the hypercalciuric action of the sodium load, which will counteract the beneficial effect of the alkali load (10).

Chronic diarrhoeal states

Chronic diarrhoea may result in low urine volume and loss of base from the intestinal tract, subsequently leading to hypocitraturia and a higher risk of calcium nephrolithiasis. Alkaline citrate is the preferred treatment in these cases (9). A fat-reduced diet and anti-diarrhoeal agents may also be indicated.

Cystinuria

Patients with cystinuria excrete increased amounts of cystine (and ornithine, lysine and arginine) in the urine due to an autosomal recessive inherited defect of membrane transport of dibasic amino acids. The symptomatology of cystinuria, stone formation, is due to the fact that cystine is highly insoluble at concentrations above 1200 μ mol/l at physiological pH. The cystine stone is usually weakly radiopaque due to the

sulphur content. Treatment of cystinuria aims at reducing urinary cystine concentration to below 1000–1200 $\mu\text{mol/l}$ and increasing urine pH. Initial treatment should always include a high fluid intake throughout the day and alkali treatment at a dose sufficient to increase urinary pH to 6.5–7.0. For this purpose sodium alkali seems less ideal, since sodium loading may promote hypercalciuria and increase the risk of calcium phosphate crystallization (10). Furthermore, it has been shown in several studies that sodium loading increases urinary cystine excretion, and that sodium restriction is anticystinuric (16). Therefore, potassium alkali should be preferred. When this combination therapy is insufficient, thiols (D-penicillamine or α -mercaptopropionylglycine) may be added to the treatment. Penicillamine treatment is frequently associated with serious side-effects, including nephrotic syndrome, dermatitis and pancytopenia. These side-effects may also occur using α -mercaptopropionylglycine. However, the side-effects of this drug seem to be less prominent (17). If the patients are intolerant to D-penicillamine and α -mercaptopropionylglycine, captopril may be tried, although the role of captopril in the treatment of cystinuria is debatable. The combination of alkali, α -mercaptopropionylglycine and captopril also has been used successfully in treatment of resistant cases (18). D-penicillamine, α -mercapto-propionylglycine and captopril all act by complexing cystine, producing a more soluble substance than cystine. Despite all these therapeutic options, medical treatment of cystinuria is often ineffective (17). Patients should be followed closely with regard to stone recurrence, renal function and drug side-effects.

Infection calculi

Infection calculi may be divided into primary and secondary infection stones. A primary infection stone refers to a condition of urinary infection with a urease-producing microorganism subsequently leading to stone formation, while a secondary infection stone refers to a primary stone, i.e. calcium oxalate, that has become infected secondarily, for instance due to vesico-ureteral reflux.

Infection with urease-producing microorganisms (*Proteus*, *Klebsiella*, *Pseudomonas* and some species of *Staphylococcus*) may lead to heavy struvite and calcium carbonate apatite stone formation. Also, urinary infection with *Ureaplasma urealyticum*, which requires special culture techniques for diagnosis, may lead to infection calculi (19). Complicated staghorn calculi that present serious clinical problems are often formed (20). The basic principle of treatment in these patients is to control the infection. To eradicate the infection it is important to clear the kidneys of any existing stone material and correct anatomical abnorm-

alities that may predispose to infection. For a discussion of the different technical treatment modalities see Segura et al. (21). Low-dose prophylactic antibiotic therapy is controversial. Residual stone material will often harbour the microorganism within its interstices, making complete eradication difficult and creating good possibilities for the bacteria to become resistant to the antibiotics used. Long-term urinary acidification with ammonium chloride has been used with success in some series (22). This treatment may be associated with gastrointestinal side-effects, and the possible risk of demineralization of bone during chronic acid loading has not yet been evaluated in this group of patients.

Anatomical/functional abnormalities

Calculus formation is more likely to occur in conditions with impaired drainage of urine from the kidney, such as ureteropelvic junction obstruction, ureteric stricture, megaureter, horseshoe kidney, vesicoureteric reflux and calyx cyst. Often secondary infection with urease-splitting organisms is involved. Treatment consists of surgical correction and eradication of infection. Pole resection or nephrectomy may occasionally be needed in order to render the patient free of infection. Medullary sponge kidney (MSK) is a rare condition, characterized pathoanatomically by ectatic collecting ducts. Diagnosis is made by intravenous urography. Risk factors for stone formation in MSK include stasis of urine in the ectatic ducts, urinary infection and metabolic defects including hypocitraturia and hypercalciuria, possibly due to the presence of incomplete RTA (23). Treatment consists of eradication of infection (in some cases prophylactic antibiotics may be needed), potassium citrate and thiazides depending on the predominant risk factor.

Treatment of MIAF urolithiasis is summarized in Table III.

IDIOPATHIC CALCIUM NEPHROLITHIASIS

Prophylactic treatment options in idiopathic calcium nephrolithiasis consists of certain conservative recommendations which can be made for all patients regardless of the underlying metabolic abnormality, and specific medical therapy for patients with "complicated" idiopathic calcium nephrolithiasis (Table II) (Fig. 1).

Conservative treatment

Stone patients often ask for advice on dietary factors that will reduce the risk of stone recurrence. Traditionally, stone patients have been encouraged to increase fluid intake, and avoid dietary excess of animal protein, calcium, oxalate, sodium and refined

sugars. The use of such a regime as sole "treatment" was shown to be effective in preventing stone recurrence in 71% of patients defined as hypercalciuric ("stone clinic effect") (24). This, as well as most other studies on dietary intervention in stone formers, suffered from the important drawback that it was not controlled.

Two controlled studies have been published recently: one testing the value of a high fluid intake (25) and the other testing the effect of a low animal protein/high fibre/high fluid diet in prevention of stone recurrence (26). Since the instruction to drink more fluid is probably the advice most universally offered to stone patients, it was fortunate that the first of these studies showed that increasing the fluid intake did indeed reduce stone recurrence rate (25).

The dietary advice of reducing protein intake in order to reduce stone recurrence is strongly supported by metabolic studies and epidemiological observations. Contrary to what should be expected from these studies, the authors of the latter controlled study were not able to show that a low animal protein/high fibre/high fluid diet had any advantage over advice to increase fluid intake alone (26). The study was performed in people who had calcium oxalate stones for the first time, and one could argue that recurrent stone formers might be more sensitive to the consequences of a high protein diet than are single stone formers (27). This study brings into question the value of reducing the protein intake for stone prophylaxis.

With regard to reducing the intake of oxalate rich foodstuffs, salt and refined sugars, there are no controlled studies to guide us, and, it is thus highly questionable whether it is justified to give stone patients such strict advice. Dietary calcium intake deserves special attention. Until recently, stone patients were often advised to avoid dairy products in order to reduce calcium intake and, hence, urinary calcium excretion. However, a recent follow-up study of over 45000 primarily healthy men provided evidence that individuals with a moderate to high dietary calcium intake had a decreased risk of symptomatic kidney stones compared with individuals with a low calcium intake (3). The pathophysiological background for this may be that by decreasing calcium intake, intestinal oxalate absorption will increase, resulting in an increase in oxalate excretion. Since a low calcium diet also may result in osteopenia (28), calcium stone formers should not be advised to reduce dietary calcium intake. Hence, the dietary advice that can be offered stone formers based on validation in controlled trials is: increase fluid intake and retain a normal dietary calcium intake. With regard to protein, salt and oxalate intake, there is no documentation for strict dietary recommendations. However, based on epide-

miological data, it seems advisable to avoid over-consumption of these foodstuffs.

Selective drug therapy in complicated idiopathic calcium nephrolithiasis

Based on the principles of evaluation presented above, only "treatable risk factors" should be looked for, and in the Nordic area the risk factors that remain in question are hypercalciuria and hypocitraturia (see below).

Idiopathic hypercalciuric calcium nephrolithiasis. The role of hypercalciuria as a significant risk factor for stone formation has been discussed extensively (1). In the Nordic area it has been demonstrated in several studies that, as a group, idiopathic stone formers consistently excrete more calcium in the urine than do a contemporary cohort of control subjects (4, 7, 29, 30). The limits of normal urinary calcium excretion should be defined in the population in question and not based solely on older studies in other populations. Traditionally, an upper limit of normal calcium excretion of 0.1 mmol/kg/24 h has been accepted. However, it is strongly recommended that each population establish their own normal limits. Hypercalciuria has been divided into absorptive and renal hypercalciuria (31). The absorptive form may be further divided into three subtypes. Not all investigators agree on such a strict subdivision. Thiazide treatment, regardless of the subtype, has been proven effective, as assessed by stone recurrence rate (follow-up period of 3 years) in placebo-controlled trials (32) and, thus, thiazides appear to be the drug of choice for patients with complicated idiopathic calcium nephrolithiasis and hypercalciuria. Current studies indicate that thiazides may have limited long-term effectiveness (33). This may be because thiazides often induce hypocitraturia secondary to hypokalaemia. Potassium supplementation may therefore be required in order to prevent hypokalaemia and hypocitraturia (34).

Thiazide treatment may be associated with significant side-effects, including hypokalaemia (and hypocitraturia), fatigue (with or without hypokalaemia), photosensitivity, impotence, hyperurecaemia, hyperglycaemia and hyperlipidaemia. Although the side-effects are often minor, in order to balance out the potential risks, the patients selected for thiazide treatment clearly should be highly motivated to undergo treatment (complicated stone disease).

Idiopathic hypocitraturic calcium nephrolithiasis. The physicochemical action of citrate on the different phases of calcium oxalate crystallization is well-documented (35). Several studies in the Nordic area have demonstrated that at least one-quarter of the idiopathic stone population are hypocitraturic (e.g.

Table III. Treatment of the most common causes of MIAF-urolithiasis (see text for details)

Underlying disease	Treatment
Defects in purine metabolism	
Uric acid nephrolithiasis	Potassium citrate
Gout	Allopurinol
Hyperoxaluric states	
Primary hyperoxaluria	High fluid intake Pyridoxine Potassium citrate
End stage renal disease	Liver and kidney transplantation Potassium citrate
Enteric hyperoxaluria	Dietary oxalate and fat restriction Potassium citrate
Hypercalcaemic states	
Primary hyperparathyroidism	Parathyroidectomy
Other hypercalcaemic states	Treatment according to underlying disease
Renal tubular acidosis (RTA)	
Type 1 (distal) RTA	Potassium citrate
Incomplete RTA	Potassium citrate
Chronic diarrhoeal states	Potassium citrate Anti-diarrhoeal agents
Cystinuria	High fluid intake Potassium citrate α -mercaptopyronylglycine D-penicillamine Captopril
Infection calculi	Clear kidney from stones Control infection
Anatomical/functional abnormalities	Surgical correction Control infection Treat metabolic defects

MIAF-urolithiasis: conditions with a definitive metabolic, infectious or anatomical/functional cause of stone formation.

urinary citrate excretion below the lower 95% confidence limit of normals, usually close to 2 mmol/24 h) (35,36). Again, the limits of normal should be established in the population in question. Hypocitratemia is often associated with a particularly active stone disease. In case of severe hypocitratemia, renal tubular acidosis should always be suspected. Treatment consists of citrate supplementation (37). Study of a metabolically unselected group of calcium stone formers in a randomized, but not placebo-controlled, trial, showed no benefit of sodium potassium citrate over general advice with regard to stone recurrence (follow-up 3 years) (38). However, in a recent placebo-controlled study, potassium citrate treatment resulted in a significantly reduced stone recurrence rate compared with placebo in a selected group of severely recurrent stone formers (complicated stone disease) with hypocitratemia (39). Thus, if citrate treatment should be expected to be effective as stone prophylaxis, the stone patients should be selected as hypocitratemic with a complicated stone disease. Furthermore, citrate should theoretically be given as the potassium salt in order to avoid the calciuric effect of sodium (10). Potassium citrate shares with other potassium salts the tendency to irritate the gastric mucosa, which may limit patient acceptability.

In clinical trials the incidence of gastrointestinal side-effects has ranged from 9% to 17% (40). Recently, a new formulation of citrate containing potassium as well as magnesium at a low ratio was developed (41) and tested in a placebo-controlled randomized trial (40). The trial was performed in metabolically unselected recurrent calcium stone formers (two or more calculi within the previous 5 years and at least one calculus within the previous 2 years). The treatment was given for 3 years, and it was shown that this new drug, potassium-magnesium citrate, reduced the risk of recurrence by 85% compared with placebo, indicating that even non-selective use of citrate salts may be beneficial (40). However, until additional long-term trials are available, the concept of selective medical management of stone patients is recommended.

CONCLUSION

These evaluation and treatment guidelines are based on the severity of the stone disease in the individual stone former. A basic metabolic evaluation is performed in all stone patients. This evaluation profile aims at diagnosing/excluding overt metabolic, infectious, anatomical or functional disorders (MIAF urolithiasis

(Table I)), which, if untreated, could result in damage to renal function and/or failure of other organ systems. Having excluded MIAF urolithiasis, patients with a simple stone disease need no further evaluation, and no other treatment than the advice to increase fluid intake and retain a normal dietary calcium intake. Patients with MIAF urolithiasis are treated according to the nature of the underlying disease (Table III). Having excluded MIAF urolithiasis in patients with a complicated stone disease, an additional extended metabolic evaluation is employed in order to diagnose patients with hypercalciuria and hypocitraturia, for which selective medical therapy has been proven effective in placebo-controlled clinical trials. The evaluation flow-chart and treatment guidelines are summarized in Figure 1.

ACKNOWLEDGEMENTS

This study was supported by grants from the Beckett Foundation and the foundation of Director Emil Hertz and Mrs Inger Hertz.

REFERENCES

- Ryall RL, Marshall VR. The investigation and management of idiopathic urolithiasis. In: Wickham JEA, Buck AC, editors. Renal tract stone. Metabolic basis and clinical practice. Edinburgh: Churchill Livingstone, 1990: 307–31.
- Goldfarb S. Dietary factors in the pathogenesis and prophylaxis of calcium nephrolithiasis. *Kidney Int* 1988; 34: 544–55.
- Curhan GC, Willett WC, Rimm EB, Stampfer MJ. A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. *N Engl J Med* 1993; 328: 833–8.
- Tiselius H-G. Metabolic evaluation of patients with stone disease. *Urol Int* 1997; 59: 131–41.
- Tiselius H-G, Larsson L. Urinary excretion of urate in patients with calcium oxalate stone disease. *Urol Res* 1983; 11: 279–83.
- Johansson G. Magnesium metabolism. Studies in health, primary hyperparathyroidism and renal stone disease. *Scand J Urol Nephrol* 1979; Suppl 51: 1–73.
- Bek-Jensen H, Tiselius H-G. Stone formation and urine composition in calcium stone formers without medical treatment. *Eur Urol* 1989; 16: 144–50.
- Osther PJ. Hyperoxaluria in idiopathic calcium nephrolithiasis. What are the limits? *Scand J Urol Nephrol*: in press.
- Preminger GM. Renal calculi: pathogenesis, diagnosis, and medical therapy. *Semin Nephrol* 1992; 12: 200–16.
- Sakhaee K, Nicar M, Hill K, Pak CYC. Contrasting effects of potassium citrate and sodium citrate therapies on urinary chemistries and crystallization of stone-forming salts. *Kidney Int* 1983; 24: 348–52.
- Pak CYC, Sakhaee K, Fuller C. Successful management of uric acid nephrolithiasis with potassium citrate. *Kidney Int* 1986; 30: 422–8.
- Leumann E, Hoppe B, Neuhaus T. Management of primary hyperoxaluria: efficacy of oral citrate administration. *Pediatr Nephrol* 1993; 7: 207–11.
- Tiselius H-G, Ahlstrand C, Lundström B, Nilsson MA. [¹⁴C]Oxalate absorption by normal persons, calcium oxalate stone formers, and patients with surgically disturbed intestinal function. *Clin Chem* 1981; 27: 1682–5.
- Osther PJ, Bollerslev J, Hansen AB, Engel K, Kildeberg P. Pathophysiology of incomplete renal tubular acidosis in recurrent renal stone formers: evidence of disturbed calcium, bone and citrate metabolism. *Urol Res* 1992; 21: 169–73.
- Preminger GM, Sakhaee K, Skurla C, Pak CYC. Prevention of recurrent calcium stone formation with potassium citrate therapy in patients with distal renal tubular acidosis. *J Urol* 1985; 134: 20–3.
- Lindell Å, Denneberg T, Edholm E, Jeppson J-O. The effect of sodium intake on cystinuria with or without tiopronin treatment. *Nephron* 1995; 71: 407–15.
- Sakhaee K. Cystinuria: pathogenesis and treatment. *Miner Electrolyte Metab* 1994; 20: 413–23.
- Chow GK, Strem SB. Medical treatment of cystinuria: results of contemporary clinical practice. *J Urol* 1996; 156: 1576–8.
- Hedelin H, Brorsson JE, Grenabo L, Pettersson S. *Ureaplasma urealyticum* and upper urinary tract stones. *Br J Urol* 1984; 56: 244–9.
- Grenabo L, Hedelin H, Pettersson S. The severity of infection stones compared to other stones in the upper urinary tract. *Scand J Urol Nephrol* 1985; 19: 285–9.
- Segura JW, Preminger GM, Assimos DG, Dretler SP, Kahn RI, Lingeman JE, Macaluso JN, McCullough DL. Nephrolithiasis clinical guidelines panel summary report on the management of staghorn calculi. *J Urol* 1994; 151: 1648–51.
- Wall I, Tiselius H-G. Long-term acidification of urine in patients treated for infected renal stones. *Urol Int* 1990; 45: 336–41.
- Osther PJ, Mathiasen H, Hansen AB, Nissen HM. Urinary acidification and urinary excretion of calcium and citrate in women with bilateral medullary sponge kidney. *Urol Int* 1994; 52: 126–30.
- Hosking DH, Erickson SB, Van den Berg CJ, Wilson DM, Smith LH. The stone clinic effect in patients with idiopathic calcium urolithiasis. *J Urol* 1983; 130: 1115–8.
- Borghetti L, Meschi T, Amato F, Briganti A, Novarini A, Giannini A. Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5 year randomized prospective study. *J Urol* 1996; 155: 839–43.
- Hiatt RA, Ettinger B, Caan B, Quesenberry CP, Duncan D, Citron JT. Randomized trial of a low animal protein, high fiber diet in the prevention of recurrent calcium oxalate kidney stones. *Am J Epidemiol* 1996; 144: 25–33.
- Osther PJ, Nørgaard JR, Engel K, Kildeberg P. Effect of acute acid loading on the risk of calcium phosphate and calcium oxalate crystallization in urine. *Scanning Microsc* 1994; 8: 63–9.
- Hess B, Casez J-P, Takkinen R, Ackermann D, Jaeger P. Relative hypoparathyroidism and calcitriol up-regulation in hypercalciuric calcium renal stone formers—impact of nutrition. *Am J Nephrol* 1993; 13: 18–26.
- Wikström B, Backman U, Danielsen BG, Fellström B, Johansson G, Ljunghall S. Ambulatory diagnostic

- evaluation of 389 recurrent renal stone formers. *Klin Wochenschr* 1983; 61: 85–90.
30. Ljunghall S, Waern AU. Urinary electrolytes in renal stone formers and healthy subjects. *Scand J Urol Nephrol* 1977; Suppl 41: 55–76.
 31. Pak CYC. Physiological basis for absorptive and renal hypercalciuria. *Am J Physiol* 1979; 237: F415–23.
 32. Ettinger B, Citron JT, Livermore B, Dolman LI. Chlorthalidone reduces calcium oxalate calculous recurrence but magnesium hydroxide does not. *J Urol* 1988; 139: 679–83.
 33. Preminger GM, Pak CYC. Eventual attenuation of hypocalciuric response to hydrochlorothiazide in absorptive hypercalciuria. *J Urol* 1987; 137: 1104–9.
 34. Pak CYC, Peterson R, Sakhaee K, Preminger GM. Correction of hypocitraturia and prevention of stone formation by combined thiazide and potassium citrate therapy in thiazide-unresponsive hypercalciuric nephrolithiasis. *Am J Med* 1986; 79: 284–8.
 35. Tiselius H-G, Fornander A-M, Nilsson M-A. Effects of citrate on the different phases of calcium oxalate crystallization. *Scanning Microsc* 1993; 7: 381–90.
 36. Osther PJ. Citrate and kidney stones. *J Dan Med Assoc* 1993; 155: 3835–9.
 37. Pak CYC, Fuller C, Sakhaee K, Preminger GM, Britton F. Long-term treatment of calcium nephrolithiasis with potassium citrate. *J Urol* 1985; 134: 11–9.
 38. Hofbauer J, Höbarth K, Szabo N, Marberger M. Alkali citrate prophylaxis in idiopathic recurrent calcium oxalate urolithiasis—a prospective randomized study. *Br J Urol* 1994; 73: 362–5.
 39. Barcelo P, Wuhl O, Servitge E, Rousaud A, Pak CYC. Randomized double-blind study of potassium citrate in idiopathic hypocitraturic nephrolithiasis. *J Urol* 1993; 150: 1761–4.
 40. Ettinger B, Pak CYC, Citron JT, Thomas C, Adams-Huet B, Vangessel A. Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. *J Urol* 1997; 158: 2069–73.
 41. Koenig K, Padalino P, Alexandrides G, Pak CYC. Bioavailability of potassium and magnesium and citraturic response from potassium-magnesium citrate. *J Urol* 1991; 145: 330–4.

Copyright of Scandinavian Journal of Urology & Nephrology is the property of Taylor & Francis Ltd and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.

Copyright of Scandinavian Journal of Urology & Nephrology is the property of Taylor & Francis Ltd and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.