

43 Medical Management of Kidney Stones: Current Recommendations

Abstract: A careful and individualized evaluation of metabolic risk factors and exclusion of anatomic renal abnormalities is a fundamental part of the medical management of the patients with kidney stones. The simplified evaluation requires a single 24-hour urine sample collected on a random diet for a complete stone risk analysis, whereas for a comprehensive evaluation three 24-hour collections are recommended for the measurements of stone risk factors that includes hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia, hypomagnesuria, uric acid and relative supersaturation with respect to calcium oxalate, calcium phosphate monosodium urate, uric acid, struvite and estimation of creatinine, ammonium and electrolytes.

Thus, an accurate diagnosis of stone disease from the tests interpretation is the basis for designing an efficient and rational therapeutic program for the medical management of kidney stones and reduction of recurrent stone formation. Potassium citrate alone or with thiazide or indapamide, combined with dietary modification and water or fluid intake more than 3 liters per day (to produce more than 2 liters of urine per day) is the most effective therapy in the management of the patients with kidney stones and prevention of further stone formation. A high animal protein diet causes hypercalciuria, hypocitraturia and bone loss confirming an acid load. Potassium-rich fruit juices increase the urinary pH and citrate by producing an alkali load.

In normal subjects, a high calcium diet does not increase the urinary saturation of calcium oxalate. Dietary oxalate restriction prevents secondary rise in urinary oxalate, thiazide or indapamide reduces the urinary calcium, potassium citrate increases the urinary the citrate and pH. The rise in urinary pH retards uric acid precipitation by increasing its solubility. Dietary calcium intake is restricted only in patients with absorptive hypercalciuria.

Identification of the stone risk factors is the key to medical management of the kidney stones and the prevention of their recurrence.

INTRODUCTION

Kidney stones vary in clinical presentation from asymptomatic to large, obstructing staghorn calculi that can significantly impair renal functions and lead to end-stage renal disease. The severity of stone disease depends on the pathogenetic factors contributing to the rate of stone formation in addition to the stone type, size, and location. In its most classic form, nephrolithiasis is manifested as renal colic. This discomfort of abrupt onset intensifies overtime into an excruciating, severe flank pain that resolves only with stone passage or removal. Stones smaller than 5 mm are likely to pass spontaneously with hydration, whereas larger stones often necessitates urologic intervention.^{1,2}

In this communication the main emphasis is on the medical diagnosis and current recommendations for the medical management of kidney stones. All patients, even those with a single stone, should undergo thorough clinical, medical and metabolic evaluation aimed at the identification of the risk factors responsible for the formation of stones.³⁻⁵

MEDICAL EVALUATION

The stone history begins with a chronology of stone events: age of incidence of first stone, size and number of stones formed, frequency of spontaneous passage of stones, stone type if known, and whether the stone occurred in both kidneys or unilaterally. Also helpful is a report of the

patient's symptoms with each episode as well as the need for and response to any surgical intervention. Calcium stone formers are either first time or recurrent stone formers.

Systemic disorders, stone risk factors (Table 1), and the medications (Table 2) that can contribute to nephrolithiasis are sought in the medical history. A number of stone disorders are inherited, making the family history an important component of the medical evaluation. Idiopathic hypercalciuria appears to be a familial disorder. Stones arising in childhood or young adulthood can be related to autosomal recessive disorders such as cystinuria, and primary oxaluria.^{6,7,8}

Occupation and lifestyle are the social aspects of the stone formation. Minimal fluid and water intake in order to avoid frequent micturition, and loss of insensible fluid as observed in building construction workers, agricultural workers, iron smiths, or excessive loss of fluids in strenuous exercise, sweating in hot climate, and gardening or in diarrheal state. The evaluation proceeds with a thorough review of the patient's diet and the fluid intakes. Patients are asked to review what they eat at all meals and snacks. Particular attention is paid to ingestion of foods high in sodium (fast foods, canned foods, added salt or soy sauce) and the quantity of animal protein consumed per day.⁹ Many patients are erroneously advised by physicians to avoid calcium-containing foods. Doing so not only may result in bone demineralization but also may increase the incidence and severity of stone formation. The various foods, which, if consumed in excess may contribute to stone formation are listed in Table 3.

A high animal protein diet can contribute to calcareous stone formation by providing a purine load, which causes hyperuricosuria.^{2,10} and urate-induced crystallization of calcium oxalate.⁹ More importantly, animal proteins contribute to the formation of calcium oxalate stones by delivering an acid load,¹⁰ which induces hypercalciuria and hypocitraturia. Uric acid stone formation is also promoted by hyperuricosuria and low urinary pH (arising from acid load). Finally, the excess acid load from animal protein may cause bone loss, a clinical feature that often accompanies stone formation.

Stone analysis should be performed in all patients, whenever possible. Knowing the constituents of a stone shall help the physician target certain elements of the medical history and is fundamental in the risk evaluation of stone formers. The stone composition is analyzed best with quantitative infrared spectroscopy (FTIR) or semi-quantitative X-ray diffraction (XRD). For uric acid/urate, cystine, and infection stones, the result of the stone analysis is inevitable, as it is for stones with an unusual composition such as indinavir, 2,8-dihydroxyoxyadenine, xanthine, triamterene, sulfadiazine, and silica. The diagnosis of cystine stones is established by a positive nitroprusside test and its chemical analysis.

Radiologic tests (KUB Films, IVP, CT Scans) can help determine the location and extent of the stone burden and may elucidate anatomical abnormalities contributing to stone formation. In general, ultrasonography is excellent in demonstrating stones within the kidney, but may miss ureteral stones.

A randomly collected spot urine sample is useful for demonstration of bacteriuria, pyuria, and hematuria, often present in active stone disease. Bacteriuria and pyuria noted in conjunction with a high urinary pH (> 6.5) are characteristic of struvite stone disease. Urine specimens for culture should be obtained in this setting. A consistently high urinary pH may also suggest calcium phosphate nephrolithiasis. Uric acid and calcium oxalate stones grow more favorably at an acidic pH. A centrifuged sample of freshly voided urine is suitable for microscopic examination of crystals. A spot urine sample also is well suited for the nitroprusside test to demonstrate cystinuria. Urine turns purple when sodium nitroprusside is added to a sample containing cystine at a concentration greater than 75 mg/L.⁴

A pH above 6.0 in uninfected morning urine or a pH that is never below 5.8 in repeated measurements during the day should raise the suspicion of defective renal acidification and the diagnosis of distal renal tubular acidosis should be established by an acid load test.^{24,25} A

standardized pH measurement can be obtained in the night urine preferably collected over 8 hours between 10 pm and 6 am (Table 4).

Protocols for Metabolic Evaluation

A protocol for patient evaluation is presented in Table 5. Three 24-hour urine samples are obtained from patients, with three corresponding blood samples drawn between 8 and 9 am in the postabsorptive state. Hypercalcemia, hypercalciuria, hyperoxaluria, hyperuricosuria, low pH, and hypocitraturia all are specifically investigated. If calcium level is elevated or at the upper limit of normal or if the serum phosphorus level is reduced or at the lower limit of normal, a serum intact PTH (parathyroid hormone) level is also determined to rule out primary hyperparathyroidism. Measurements of serum $1,25(\text{OH})_2\text{D}_3$, low molecular weight proteinuria are performed as necessary.

It might be of interest on occasion to distinguish between the different types of absorptive hypercalciuria. Type I is associated with increased urinary calcium, regardless of calcium intake, while type II patients have hypercalciuria only with high dietary calcium. In type III absorptive hypercalciuria, the increased absorption of calcium is mediated by the $1,25(\text{OH})_2\text{D}_3$ caused by hypophosphatemia.

Stone Risk Diagnostic Profile

A careful and individualized evaluation of recognized risk factors for kidney stone formation¹¹ is a fundamental part of the management of patients with urinary tract stone disease. This profile provides a visual graphic display of quantitative test analysis for metabolic, environmental, physicochemical and nutritional risk factors and the derangements responsible for the formation of stones and their clinical implications. Based on test results each risk factor is plotted on a graphic display (Fig. 1) in such a manner that each risk factor is easily identified as an increased risk (abnormal; shown in yellow) or reduced risk (normal; shown in blue). The horizontal midpoint line located in the centre of the graphic display provides established upper and normal limits for each risk factor for quick reference. For the purpose of providing a visual display of all available data in one report, each factor is assigned a vertical line with a linear or logarithmic scale.

The most significant benefit of the visual graphic display is "instantaneous interpretation" of:

- A. The abnormalities responsible for stone formation or contributing to the patient's tendency to form stones (Fig 1). Risk factors with values above the "normal values line" on the graph indicate an abnormality or increased risk and the risk factors with values below the "normal values line" on the graph indicate a normal condition or reduced risk.
- B. And to make an accurate diagnosis of stone disease from the test's interpretation, as a basis for designing an efficient and rational therapeutic program.

Table 6 summarizes the final interpretation of the results of medical and metabolic evaluation of the patients with the stone disease, which makes the basis for selective and effective therapy.

CURRENT RECOMMENDATIONS FOR MEDICAL MANAGEMENT OF KIDNEY STONES

A. Conservative Treatment: Diet Modification and Increased Fluids

Limited Intake of Animal Proteins

It is important to balance the intake of animal proteins with ingestion of potassium-rich fruit products, so that the excessive acid load from the former can be neutralized by alkali delivered by the latter. High animal protein intake may be gauged from increased urinary sulfate and uric acid, and reduced urinary pH. Acid load may be gauged from reduced urinary pH and citrate, and increased urinary ammonia.

Dietary Sodium Restriction

A high sodium intake may exaggerate stone formation by increasing urinary calcium, promoting sodium urate-induced crystallization of calcium oxalate, and by reducing urinary citrate (from induction of mild metabolic acidosis).¹² The recommended sodium intake is 100 mEq/day or about 1 teaspoonful of table salt/day.

Adequate Ingestion of Potassium-Rich Fruit Products

Potassium-rich fruit products are preferable to potassium-poor fruit products for reasons previously enumerated. Fruit products in the form of juices are particularly useful owing to their fluid content. Hypocitraturia in the setting of low urinary potassium suggest inadequate intake of potassium-rich citrus fruits.

High Fluid Intake

The intake of fluid (in all forms) should be sufficient to ensure urine output of at least 2 L/day. In the absence of diarrhea or excessive sweating, the above goal may be achieved by ingestion of 3 L fluids/day. Fluids should be consumed in divided amounts throughout the day.

Dietary Oxalate Restriction

When urinary oxalate is high normal (30-44 mg/day), moderate oxalate restriction should be applied by limiting the intake of oxalate-rich foods (Table 3). Intake of ascorbic acid should be <500 mg/day, since this vitamin is a substrate for oxalate synthesis.

Dietary Calcium Restriction

Among patients with normal serum calcium and intestinal calcium absorption, calcium restriction is not necessary. However, dietary calcium restriction is necessary in patients with absorptive hypercalciuria. Urinary calcium excretion increases steeply with a rise in calcium intake, at a level much higher than in normal subjects.¹³ Thus, a satisfactory control of hypercalciuria may not be achieved unless calcium intake is limited to about 400-600 mg/day. It is critical that dietary oxalate intake is restricted as well in order to avert the secondary rise in oxalate excretion.

Dietary and Pharmacologic Treatment

Patients with uncomplicated calcium oxalate nephrolithiasis are separated into normocalciuric and hypercalciuric variants. In the former, the treatment comprises potassium citrate alone. The latter group, potassium citrate is given together with thiazide or indapamide.

Potassium Citrate in Normocalciuric Calcium Oxalate Nephrolithiasis

By providing an alkali load, potassium citrate increases urinary citrate and pH. Unlike sodium citrate, potassium citrate produces a transient decline in urinary calcium. Induced hypocitraturia inhibits nucleation and agglomeration of calcium oxalate, as well as urate-induced heterogeneous nucleation of calcium oxalate. The rise in urinary pH retards uric acid precipitation by increasing its solubility. Thus, potassium citrate is effective in the prevention of stone formation in hypocitraturic calcium nephrolithiasis, distal renal tubular acidosis, chronic diarrheal state, hyperuricosuric calcium nephrolithiasis, and gouty diathesis.¹⁴

Potassium Citrate + Thiazide or Indapamide in Absorptive Hypercalciuria

The pharmacologic intervention plus dietary modification is recommended for the optimum management of absorptive hypercalciuria.^{15,16}

- Dietary calcium restriction: controls hypercalciuria
- Dietary oxalate restriction: prevents secondary rise in urinary oxalate
- Thiazide or indapamide: reduce urinary calcium
- Potassium citrate: increases urinary citrate. This treatment has also been shown to prevent hypokalemia induced by diuretic therapy.

This approach has shown promise in a recent study.¹⁵⁻¹⁶ Urinary calcium significantly declined, from dietary calcium restriction and treatment with calcium-sparing diuretic. Urinary oxalate did not increase owing to dietary oxalate restriction. Urinary saturation of calcium oxalate significantly declined, and new stone formation virtually ceased. In normal subjects, a high calcium diet does not increase urinary saturation of calcium oxalate, since the modest increase in urinary calcium is overcome by reduced urinary oxalate and increased citrate. In stone-formers many of whom suffer from increased intestinal calcium absorption, urinary calcium is equally effective as urinary oxalate in increasing the urinary saturation of calcium oxalate.

Current conservative and drug recommendations for medical management of kidney stones are summarized in Tables 7 and 8. The identification of stone risk factors is the key to effective medical management of kidney stones and their recurrence.

REFERENCES

1. Monk RD, Bushinsky DA. Nephrolithiasis and nephrocalcinosis. In: Johnson R, Fehally J, eds. *Comprehensive Clinical Nephrology*. London, Mosby 2000:973-89.
2. Coe FL, Parks JH, Asplin JR. The pathogenesis and treatment of kidney stones. *N Engl J Med* 1992; 327:1141-52.
3. Teotia SPS, Teotia M. Environmental studies of endemic fluorosis, goitre and stone and their epidemiological interrelationships-Major breakthrough in environmental research and its technical impact on safe drinking water supplies to villages. Technical Report. Government of India, Ministry of Environment and Forests. 1990;1-91.
4. Teotia M, Teotia SPS. Pediatric Nephrolithiasis. In: Wickham JEA, Buck AC, eds. *Renal Tract Stone-Metabolic basis and clinical practice*, 1st edition, London, Churchill Livingstone 1990:439-49.
5. Teotia M, Teotia SPS. Kidney and bladder stones in India. *Postgrad Med J* 1977;53:41-8.
6. Sakhaee K. Pathogenesis and medical management of cystinuria. *Semin Nephrol* 1996;16:435-47.
7. Danpure CJ, Smith LH. The Primary Hyperoxalurias. In: Coe FL, Favus MJ, Pak CYC, et al. eds. *Kidney Stones: Medical and Surgical Management*. Philadelphia, Lippincott-Raven 1996;859-81.
8. Teotia M, Sutor DJ. Crystallisation of ammonium acid urate and other uric acid derivatives of urine. *Brit J Urol* 1971; 43:381-6.
9. Teotia M, Teotia SPS. Urinary tract calculi in northern India-Diagnostic and therapeutic aspects. In: Singh PP, Pendse AK (Eds). *Multidimensional approach to urolithiasis*, Urolithiasis Society of India 1987;35-56.
10. Hesse A, Tiselius HG, Jahnen A. *Urinary stones: diagnosis, treatment and prevention of recurrence*. Basel (CH): S. Karger, 1997;24-202.
11. Teotia SPS, Teotia M. Clinical and Metabolic Evaluation of Stone Formers. In: Teotia SPS, Teotia M (Eds). *Nutritional and Metabolic Bone and Stone Disease: Asian Perspective*. CBS Publishers, New Delhi, 2008;786-94.
12. Sakhaee K, Harvey JA, Padalino PK, Whitson P, Pak CYC. Potential role of salt abuse on the risk for kidney stone formation. *J Urol* 1991; 150:310-2.
13. Heller HJ, Doerner MF, Brinkley LD, Adams-Huet B, Pak CYC. Effect of dietary calcium on stone-forming propensity. *J Urol* 2000; 169: 470-4.
14. Pak CYC, Fuller C, Sakhaee K, Preminger G, Britton F. Long-term treatment of calcium nephrolithiasis with potassium citrate. *J Urol* 1985;134:11-9.
15. Teotia SPS, Teotia M. Medical Management of Nephrolithiasis. In: Teotia SPS, Teotia M (Eds). *Nutritional and Metabolic Bone and Stone Disease: Asian Perspective*. CBS Publishers, New Delhi 2008; 861-70.
16. Pak CYC, Britton Faye A. Recent Developments and Current Recommendations for the Metabolic Management of Nephrolithiasis. In: Teotia SPS, Teotia M (Eds). *Nutritional and Metabolic Bone and Stone Disease: Asian Perspective*. CBS Publishers, New Delhi 2008;853-60.

MULTIPLE CHOICE QUESTIONS

1. Which is the commonest cause of stone formation?

- A. High urinary oxalate
- B. Low urinary magnesium
- C. Low urinary sodium

2. In renal tubular acidosis:

- A. Urine pH is low
- B. Urine pH is high
- C. Serum chloride is low

3. Which of the following is normal?

- A. Urinary oxalate > 40 mg/day
- B. Urinary uric acid is <800 mg/day
- C. Urinary citrate is <100 mg/day

4. Animal flesh protein:

- A. Decreases urinary citrate
- B. Increases urinary citrate
- C. Increases urinary pH

5. Dietary calcium is restricted in:

- A. Absorptive hypercalciuria
- B. Resorptive hypercalciuria
- C. Renal hypercalciuria

6. Treatment with thiazide:

- A. Reduces urinary calcium
- B. Increases urinary calcium
- C. Increases urinary magnesium

7. Potassium citrate:

- A. Increases urinary pH
- B. Provides acid load
- C. Is treatment of cystinuria

8. Vitamin-D can cause:

- A. Calcium stone
- B. Uric acid stone
- C. Xanthene stone

1. A 2. B 3. B 4. A 5. A 6. A 7. A 8. A