

Preventive Kidney Stones: Continue Medical Education

Abstract

Nephrolithiasis is a common health problem across the globe with a prevalence of 15%–20%. Idiopathic hypercalciuria is the most common cause of nephrolithiasis, and calcium oxalate stones are the most common type of stones in idiopathic hypercalciuric patients. Calcium phosphate stones are frequently associated with other diseases such as renal tubular acidosis type 1, urinary tract infections, and hyperparathyroidism. Compared with flat abdominal film and renal sonography, a noncontrast helical computed tomography scan of the abdomen is the diagnostic procedure of choice for detection of small and radiolucent kidney stones with sensitivity and specificity of nearly 100%. Stones smaller than 5 mm in diameter often pass the urinary tract system and rarely require surgical interventions. The main risk factors for stone formation are low urine output, high urinary concentrations of calcium, oxalate, phosphate, and uric acid compounded by a lower excretion of magnesium and citrate. A complete metabolic workup to identify the risk factors is highly recommended in patients who have passed multiple kidney stones or those with recurrent disease. Calcium oxalate and calcium phosphate stones are treated by the use of thiazide diuretics, allopurinol, and potassium citrate. Strategies to prevent kidney stone recurrence should include the elimination of the identified risk factors and a dietary regimen low in salt and protein, rich in calcium and magnesium which is coupled with adequate fluid intake.

Keywords: Calcium oxalate, idiopathic hypercalciuria, nephrolithiasis, prevention, risk factors

Introduction

Nephrolithiasis is a common disease with increasing prevalence of up to 20% all over the globe.^[1] The increased prevalence of the disease is due to the lifestyle changes such as lower dietary intake of vegetables or fruit, higher consumption of animal proteins, salt, sweetened beverages, and inadequate fluid intake.^[2-6] Calcium stones are the most common type of nephrolithiasis and can be associated with hyperoxaluria or hyperuricosuria.^[1,2,7]

Hypercalciuria is defined as increased urinary calcium excretion >4 mg/kg/day [Table 1] or a urinary calcium to creatinine ratio of >0.2 [Table 2]. It occurs in up to 60% of patients with recurrent calcium stones.^[1,2,4]

Hyperoxaluria is defined as an increase in urinary oxalate excretion higher than 45 mg/day [Table 2]. Hyperoxaluria occurs in 10%–30% of calcium stone formers. Urinary oxalate is primarily derived from the metabolism of glycine and ascorbic acid.^[1,2] Hyperoxaluria can also occur

following large doses of Vitamin C therapy [Table 1].

Calcium phosphate stones are due to an excessive excretion of phosphate from bone and protein metabolism. Calcium oxalate and uric acid stones tend to form in relatively acid urine (pH <5.5) while calcium phosphate stones form in alkaline urine pH >7.0.^[8,9]

There is a positive family history of nephrolithiasis in about half of the patients present with idiopathic hypercalciuria nephrolithiasis.^[10,11]

For these reasons, patients with calcium phosphate stones should be evaluated for conditions associated with alkaline urine such as distal renal tubular acidosis (type 1), urinary tract infection, and hyperparathyroidism.^[12]

Hyperuricosuria is defined as urinary uric acid excretion >750 mg/24 h, and it accounts for 20%–25% of patients with recurrent calcium stones [Table 1]. Blood uric acid levels are normal in over 80% of these patients. Uric acid stone prevalence is increasing because of increasing incidence of obesity, metabolic syndrome, and high

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purine diet rather than a defect in uric acid metabolism or reduced tubular reabsorption of uric acid.^[13] Other risk factors are reduced fluid intake and metabolic acidosis associated with acidotic urine pH.^[14-16]

Struvite stones occur in patients with history of recurrent urinary tract infections due to urease-producing organism such as proteus and klebsiella. The stones can grow rapidly to form staghorn calculus.^[17,18] The staghorn calculi are composed of magnesium ammonium phosphate and calcium carbonate apatite when ammonia production is increased and urine pH is alkaline.^[18]

Cystinuria is defined as urinary cysteine excretion >300 mg/day [Table 1]. Cystinuria is a hereditary autosomal recessive disorder of defective transport of four amino acids including cystine, ornithine, arginine, and lysine.^[19]

Laboratory Evaluation

Patients manifesting with flank pain radiating to groin, and nausea and vomiting should be evaluated for the possibility of nephrolithiasis. A routine urinalysis, complete blood count, and measurement of serum electrolytes, blood urea nitrogen, creatinine, calcium, phosphate, uric acid, and albumin concentrations are helpful to assess renal function status of the patient.^[1,2,12,17]

To evaluate the presence or absence of metabolic syndrome causing nephrolithiasis 2 or 3 separate 24 h urine collections should be obtained for calcium, oxalic acid, phosphate, uric acid, cysteine, and creatinine concentrations.^[2,17]

The diagnosis of nephrolithiasis is suspected by the clinical presentation of nausea, vomiting, severe abdominal and flank pain and hematuria with crystalluria and is confirmed radiologically.^[19]

A flat abdomen X-ray and/or abdominal sonography should be done initially which can detect the majority of kidney stones but X-ray alone may miss small stones and will not detect radiolucent uric acid stones.^[1,2,12,17] If the flat plate of abdomen is negative, a noncontrast-enhanced helical computed tomography (CT) scan of the abdomen is indicated. The noncontrast CT scanning is the diagnosis of choice to ensure when there is a possibility of uric acid stones with specificity and sensitivity of nearly 100%.^[20]

Strategies to Prevent Developing Kidney Stone

- Low dietary calcium intake is an important risk factor for formation of calcium stones and should be avoided in patients with hypercalciuric stones [Table 3].^[1-3,14] A diet poor in calcium increases intestinal oxalate absorption and increases the urinary oxalate excretion
- High dietary protein intake increases the daily acid load by generating sulfuric acid from sulfur-containing amino acid metabolism.^[21,22] The production of acid along with uric acid from protein metabolism results in increased urinary calcium and uric acid excretion and decreased

Table 1: Normal urinary solute excretion

Solute	Normal value
Calcium	<4 mg/kg/day
Oxalate	<2 mg/kg/day
Uric acid	<35 mg/kg/day
Cystine	<75 mg/g creatinine
Citrate	<180 mg/mg creatinine
Creatinine	10-20 mg/kg/day

Table 2: Random spot urine calcium to creatinine ratio

Age	Calcium/creatinine ratio
<6 months	<0.8
7-12 months	<0.6
>1 year	<0.2

Table 3: Kidney stone risk factors

Decreased urinary protective inhibitors	Increased urinary solute excretion
Low citrate excretion	High urine osmolality
Low magnesium excretion	Dehydration
Low pyrophosphate excretion	High intake of salt, oxalate, and Vitamin D
	Chronic urinary tract infection
	Obstructive hydronephrosis

urinary pH and citrate excretion leading to stone formation.^[21,22] Lowering protein intake to <1.0 g/kg/day in patients with recurrent stone formation is highly recommended in the management of these patients

- High dietary salt intake >3.0 g/day can promote stone formation by increasing the urinary calcium excretion^[4]
- Low fluid intake, dehydration, and high urine osmolality are also important risk factors for the development of nephrolithiasis by increasing the concentration of calcium and oxalate.^[4,14,16] Sweetened beverages acidified with phosphoric acid may increase the risk for developing stone and should be avoided^[7,23]
- High dietary Vitamin C intake is also considered a risk factor for calcium oxalate stones by increasing the urinary oxalate excretion^[24]
- Low urinary citrate is a major risk factor of calcium stone formation. It occurs in about 20%–25% of patients with recurrent calcium nephrolithiasis.^[2,24] Citrate in the urine combines with calcium and form a soluble complex. As result, less free calcium is available to form calcium oxalate stones.^[2] Hypocitraturia is defined as urinary citrate excretion of <320 mg/day [Table 2].^[24] The principal determinant of urinary citrate excretion is acid-base disorders. Chronic acidosis increases the proximal tubular reabsorption of citrate and lowers the urinary citrate excretion.^[2] Many clinical conditions may be associated with hypocitraturia including renal tubular acidosis, use of carbonic anhydrase inhibitors, and chronic diarrhea with acidosis^[12,21]

- Magnesium is a potent protective inhibitor of calcium stone formation [Table 2].^[25] Magnesium-rich foods such as spinach, almond, yogurt, dark leafy greens, and beans, are likely to inhibit the formation of calcium crystals.^[25]

Management of Kidney Stones

General considerations

High fluid intake to >2 L/day coupled with reduced salt and protein intake are considered the cornerstone of prevention of all forms of stone formation.^[3,4,14,16,17,21,22] Intravenous (IV) hydration with 0.9% saline and IV analgesic such as nonsteroidal anti-inflammatory drugs or morphine are indicated in patients who cannot tolerate oral fluid or medication to relieve the renal colic attacks.^[2,17] Reduction in the consumption of sweetened beverages also significantly decreases the risk of stone formation.^[23] The effectiveness of protein restriction has been evaluated in several studies. Attacks of renal colic can be managed with analgesics to relieve the pain and increased fluid intake at first. Both parenteral nonsteroidal inflammatory drugs and narcotics have been used for pain control.^[2] Stones 4 mm in diameter or smaller usually pass spontaneously and can be managed expectantly for up to 2 weeks. Staining the urine with gauz may increase the chance of recovering a small stone for chemical analysis. Stones 5 mm or larger stones that do not pass in several days must be referred to a urologist. Intervention, most commonly with shock wave lithotripsy, endoscopic lithotripsy, open lithotomy, or percutaneous nephrolithotomy is indicated in patients with continued severe pain, bleeding, obstruction, or serious infection.^[2,17,21]

Uric acid stones can be dissolved with oral alkalinizing medications such as potassium bicarbonate or potassium citrate.^[26] The prevention of this type of stone is based on the long term taking of oral citrate.^[21,25,27,28] Calcium stone formation can be prevented by the use of different including thiazide diuretics, allopurinol, phosphates, and potassium citrate.^[29] Citrates are generally safe and do not have any potentially serious side effects and may have a favorable influence on lower bone density, which is frequently observed in the calcium stone patients, but they are poorly tolerated due to their gastric effects.^[25,27,28]

The use of thiazides is, however, limited because of the fear of long-term side effects such as hypokalemia, impaired glucose balance, and increasing serum cholesterol and uric acid levels.^[29] Allopurinol may cause severe hypersensitive reactions rarely.^[30]

Specific treatments

Treatment of idiopathic hypercalciuric stones consists of the use of thiazide diuretics (1–2 mg/kg/day), adequate fluid intake (>2 L/day) dietary salt restriction (<3 g/day) and potassium citrate 1–3 mEq/kg/day.^[4,16,25,27-29]

Treatment of cystine stones should include alkalinization of urine (pH above 7.0) to increase the solubility of cystine below 300 mg/day.^[25,27,28] This can be achieved by administration of potassium citrate 3–4 mEq/kg/day and bicarbonate with or without acetazolamide.^[25,27,28] Penicillamine 1–2 g/day has been used in the refractory cases of cystinuria who have failed to response to hydration and alkaline therapy.^[19] However, its use has been associated with major side effects including nephrotic syndrome.^[19]

Medical management of struvite stones include eradication of the infection and correction of any metabolic abnormalities followed by surgical interventions for stone removal including shock wave lithotripsy or lithotomy.^[7,18,31]

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Clinical Quiz

A 15-year-old female presents to the emergency room with a dull flank pain radiating into the right thigh for 4 h. The pain was associated with nausea and vomiting but no chills, fever, dysuria, or urgency. She weighs 60 kg, blood pressure 129/87 mmHg, respiration 17/min, and the temperature 37°C. The chest is clear, and the heart is normal. The abdomen is soft, nontender, slightly distended with hypoactive bowel sounds. There is moderate costovertebral angle tenderness on the right side. Laboratory studies showed Hb 12 g/dl, Hc 37%, white blood cell 7100 cells/ μ l, sodium 138 mEq/l, potassium 4 mEq/l, chloride 102 mEq/l, bicarbonate 26 mEq/l, blood urea nitrogen (BUN) 18 mg/dl, and creatinine 0.8 mg/dl. Urinalysis revealed pH 5.0; specific gravity 1.020; 3+ bloods; trace protein; no glucose; many red blood cells; and multiple calcium oxalate crystals.

1. Which of the following studies is most likely to provide the correct diagnosis and should be done first in this situation?

- A. Noncontrast-enhanced helical computed tomography (CT) scan
- B. Abdominal plain film
- C. Intravenous pyelogram (IVP)
- D. Ultrasonography.

The helical CT scan demonstrates a 3 mm stone in the right ureter. A similar finding was seen on the abdominal flat plate.

2. Which of the following is the likely diagnosis?

- A. Calcium phosphate nephrolithiasis
- B. Calcium oxalate nephrolithiasis
- C. Uric acid nephrolithiasis
- D. Cystine nephrolithiasis.

3. What would be the best management approach at this time for this patient? (Select all that apply)

- A. Urology consultation
- B. Hospitalization
- C. Intravenous fluids
- D. Intravenous antibiotics
- E. Intravenous analgesics.

The patient experienced significant pain relief after intravenous analgesics and tolerated oral medications and fluids.

4. What orders would you write now? (Select all that apply)

- A. Hospitalization
- B. Discharge to home
- C. Low calcium diet
- D. Maintain increased oral fluid intake
- E. Strain the urine
- F. Schedule a follow-up IVP for the following week
- G. Schedule a 24-h urine collection for calcium and creatinine.

The patient was discharged and passed the stone 5 days later. No evidence of residual stone was seen on follow-up abdominal flat plate and CT scan. Analysis of the stone revealed it to be composed of 100% calcium oxalate. He now returns to the clinic to receive the results of the X-rays and stone analysis and to discuss prognosis and therapy.

5. What is your recommendation to patient at this time? (select all that apply)

- A. complete metabolic workup followed by appropriate treatment of any abnormalities and risk factors which are identified
- B. Measure the serum calcium and continue the high fluid intake but no other specific workup or therapy as the likelihood of a second stone is less than 50% at 10 years
- C. Both of the above
- D. None of the above.

The patient elected to take a conservative approach and not undergo extensive testing or specific therapy. He did increase his fluid intake to approximately 2.5 L/day for several years and then paid less attention to his intake. He was clinically stone free for 5 years until 6 weeks ago when he again experienced right-sided flank pain and hematuria and passed another small calcium oxalate. Follow-up IVP was normal, and he was referred to the clinic for further evaluation. He is on no medications, and his usual fluid intake is approximately 1.5 L/day. He now agreed to undergo metabolic evaluation.

6. Which of the following studies should be included in this evaluation? (select all that apply)

- A. 24-h urine for calcium
- B. 24-h urine for uric acid
- C. 24-h urine for oxalate
- D. 24-h urine for citrate
- E. 24-h urine for cystine
- F. 24-h urine for creatinine
- G. 24-h urine for phosphorus
- H. Serum calcium
- I. Serum uric acid
- J. Serum albumin
- K. Serum creatinine
- L. Serum electrolytes.

To maximize the sensitivity of these measurements, the values for the metabolic work-up were obtained as the mean of three, 24-h urine collection as follow:

Serum Ca: 9.8 mg/dl, Na: 149 mEq/l, K 4.0 mEq/l, Cl 105 mEq/l COH₃-25 mEq/l BUN 12 mg/dl, creatinine 0.9 mg/dl. Urine Ca: 343 mg/day (normal <300 mg/day), Na; 226 mEq/day, oxalate 33 mg/day (normal <45 mg/day), citrate 256 mg/day (normal >320 mg/day), urate 678 mg/day (normal <800 mg/day) and creatinine 1500 mg/day (normal 20 mg/kg/day).

7. What is the most appropriate therapeutic regimen for this patient at this time? (Select all that apply)

- A. Hydrochlorothiazide
- B. Potassium citrate
- C. Allopurinol
- D. Low calcium diet
- E. Moderate dietary sodium restriction
- F. High protein diet
- G. Water intake >2 L/day.

The patient was begun on thiazide diuretic, potassium citrate, increased fluid intake, and moderate sodium restriction. She returns 2 weeks later to review test results. Serum electrolytes are normal. The 24-h urine values are Sodium 205 mEq, calcium 275 mg, citrate 544 mg, oxalate 30 mg, creatinine 1450 mg, and uric acid 680 mg.

8. What do you recommend now?

- A. Reemphasize the need for restriction
- B. Add furosemide
- C. Add amiloride sodium.

The patient took his medication as instructed and maintained a high fluid intake and moderate sodium restriction. On this regimen, he remained stone-free for the next 10 years. He indicates that his brother is concerned about the possibility of an increased risk of calcium stone in the family.

9. Is there an increased risk for family members?

- A. Yes
- B. No.

Quiz Answers

- 1. A
- 2. B
- 3. B, C and E
- 4. B, D and E
- 5. A and B and C
- 6. A, B, C, D, F, H, J, K and L
- 7. A, B, E and G
- 8. A
- 9. A.