Review Article

Nephrolithiasis: Endocrine evaluation

Salam Ranabir, Manash P. Baruah[1], K. Reetu Devi[2]

Department of Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, [1]Department of Endocrinology, Excel Center, Guwahati, Assam, [2]Department of Physiology, Jawaharlal Nehru Institute of Medical Sciences, Imphal, Manipur, India

ABSTRACT

Nephrolithias is a common problem in populations around the world, and contribute significantly to the development of end stage renal disease. It is a matter of debate whether the metabolic factors responsible for renal stone formation are similar or variable in different populations around the globe. This review discusses the influence of different metabolic and dietary factor, and some other co-morbid conditions on the etiopathogenesis Nephrolithiasis. Evaluation and medical management of Nephrolithiasis is summarized in the later part of the article.

Key words: Hypercalciuria, hyperparathyroidism, nephrolithiasis, renal stone

Introduction

Nephrolithiasis is a common problem with the life-time risk around 12% in men and 6% in women, in the United States.[1,2] The overall prevalence of inpatient nephrolithiasis remained stable around 5% in the US from 1998 to 2003, but the male : female ratio decreased from 1.6 : 1 to 1.2 : 1.[3] Scales *et al*., also reported a dramatic increase in prevalence among females.[4] The incidence peaked in the third and fourth decades, and prevalence increased with age until approximately the age of 70 years.[2] Importantly, kidney stones were a recurrent disorder, with lifetime recurrence risks reported to be as high as 50%.[5,6] It may lead to end-stage renal disease in around 0.6 - 3.2%.[7-9]

Numerous factors determine the prevalence of stones, including age, race, and geographic distribution. In the United States (US), African Americans, Latin Americans, and Asian Americans are much less likely to have stones than whites.[10]

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.93740

However, all racial groups demonstrate a remarkable similarity in the incidence of the underlying metabolic abnormalities.[11] The geographical location also appears to influence stone formation. Sun exposure can lead to more concentrated urine by increasing insensible fluid losses due to sweating and can also stimulate vitamin D production, resulting in intestinal calcium absorption and urinary calcium excretion.[10] The geographic location and genetic predisposition can also influence the type of stone formed.[10,12]

In the US the various types of renal stones seen are, mixed calcium oxalate and calcium phosphate (37%), Calcium oxalate (26%), Calcium phosphate (7%), Uric acid (5%), Struvite (22%), and Cystine (2%).[13] Calcium oxalate is also the most common stone reported in India.[14-16]

Risk Factors for Stone Formation

Risk factors for urolithiaisis are generally divided into non-dietary, dietary, and urinary.

Non-dietary

Family history — The risk of urolithiaisis is greater in individuals with a family history of stone disease.[17] It is estimated to be more than 2.5 times greater in those individuals.[18] A combination of genetic predisposition as well as similar environmental exposures may be the cause for it. A polygenic inheritance has been proposed

Corresponding Author: Dr. Manash P. Baruah, Department of Endocrinology, Excel Center (Unit of Excel Care Hospitals), Ulubari, Guwahati – 781 007, Assam, India. E-mail: manashbaruahinin@yahoo.co.in

to account for the familial tendency.[19] However, there is limited information on the genes that contribute to the risk of the common forms of stone disease.

Anatomic abnormalities that result in urinary stasis such as ureteropelvic junction obstruction, horseshoe kidney or polycystic kidney may precipitate or worsen stone formation.[20]

Systemic disorders such as primary hyperparathyroidism are associated with an increased risk of formation of calcium containing stones. Primary hyperparathyroidism may be found in 5% of the stone formers.[21]

A number of other common conditions have also been linked to nephrolithiasis [Table 1]. Increasing body mass index (BMI) is associated with an increasing risk of stone formation, independent of other risk factors, including diet. The magnitude of increase in the risk from BMI is higher in women than in men. Those with BMI ≥ 30 kg / m^2 have 30% higher risk among men, but there is nearly a two-fold higher risk among women compared to those with a BMI of 21 – 23 kg / m^2.[22]

A history of gout increases the likelihood of forming kidney stones, both uric acid and calcium oxalate. In the National Health and Nutrition Examination Survey (NHANES) III, a prevalence of previous kidney stones in subjects with reported gout was 13.9%.[23] When examined prospectively, a history of gout was associated with a doubling of the risk of forming a stone, independent of diet, weight, and medications.[24]

Diabetes mellitus also increases the risk of stone formation, independent of diet and body size. In a prospective epidemiological study that involved three large cohorts in the United States, the Nurses' Health Studies I and II, and the health Professionals Follow-Up study in men, a higher prevalence of a history of kidney stones was observed in patients with diabetes compared to those without diabetes.[25] In a cross-sectional study, Meydan *et al*., observed a prevalence of stone disease of 21% in patients with diabetes, as compared to 8% in patients without diabetes.[26] The insulin-resistance results in defective renal ammonia genesis and low urine pH,[27,28] therefore, may be expected to favor the production of uric acid stones, as low urine pH has been shown to be a major lithogenic factor in idiopathic uric acid nephrolithiasis.[29-31] Insulin has been shown to enhance uric acid and sodium reabsorption in the proximal convoluted tubule, resulting in hyperuricemia, decreased uric acid, and sodium excretion.[32-34]

Environmental factors — Individuals working in a hot environment appear to be at a higher risk for kidney stone formation.[35] Situations leading to a lower fluid intake have a higher risk of stone formation.

Table 1: Factors associated with increased stone risk

Systemic diseases / factors associated with increased stone risk	Underlying mechanism(s)
Primary hyperparathyroidism	Hypercalciuria and hypercalcemia
Urinary tract infection	Precipitation of calcium phosphate and magnesium ammonium phosphate(struvite stones) in alkaline urine because of excessive ammonia production
Chronic inflammatory bowel disease	Increased oxalate absorption leading to hyperoxaluria
Ileostomy	Bicarbonate and fluid losses from intestine causing low urine volume which is acidic
Prolonged immobilization	Hypercalciuria from bone loss and urinary stasis due to bladder dysfunction in spinal injury

Dietary factors

Several dietary factors have been proposed to modify the risk of Nephrolithiasis [Box 1]. The nutrients that have been implicated include calcium, animal protein,[36] oxalate,[37] sodium,[38] sucrose,[39,40] fructose,[41] fluoride,[42] and a deficiency of magnesium,[43,44] and potassium.[45]

Calcium — In a prospective study of dietary factors and the risk of incident stone disease performed in a cohort of more than 50,000 male health professionals aged 40 to 75 years, men with a higher intake of dietary calcium had a lower risk of incident nephrolithias independent of other risk factors.[46] A similar finding has been reported in other studies.[47,48]

Low calcium intake is known to increase oxalate absorption and urinary excretion.[49] Furthermore, low dietary calcium intake may increase the risk of stone formation, even among individuals with a family history of stones.[18]

In a randomized trial, Borghi *et al*., compared a low calcium

Box 1: Dietary risk factors associated with increased stone risk

- Low fluid intake
- High intake of animal protein
- High dietary sodium
- Excessive intake of refined sugars
- Foods rich in oxalate
- High intake of grapefruit juice
- Fluoride
- Low calcium intake

BOX 1: References [Curhan *et al*.], [Breslau *et al*.],[56], [Kaul], [Holmes], [Curhan *et al*.], [Singh *et al*.], [Borghi *et al*.]

diet (400 mg / d) to a diet containing1200 mg of calcium, along with low sodium and low animal protein intake, in men with hypercalciuria and calcium oxalate stones. The recurrence of nephrolithiasis was reduced by 50% in the higher calcium intake group.[50]

The Nurses' Health Study I showed intake of dietary calcium was inversely associated with risk for kidney stones and intake of supplemental calcium was positively associated with the risk. The differential effect may be due to the timing of calcium ingestion relative to oxalate consumption.[46] However, the Nurses' Health Study II reported that supplemental calcium did not increase the risk of stone formation.[47]

Oxalate — Up to one-third of the patients with calcium oxalate nephrolithiasis may have increased absorption of dietary oxalate, and in some cases a deficiency of oxalate degradation by the bacterium Oxalobacter formigenes in the gut, may be the culprit.[51]

Other nutrients — Several other nutrients have been implicated in the development of stone formation. High animal protein intake leads to increased calcium and uric acid excretion as well as decreased urinary citrate,[52] all of which increase the risk of stone formation. An increased risk of stone formation has been observed for higher animal protein intake, only among men with BMI < 25 kg / m^2.[48] Prospective studies demonstrate that sucrose is associated with an increased risk in women[39,40] and higher dietary potassium intake is associated with a decreased risk.[43,48] Low potassium levels can promote hypocitraturia.[53] Of late, phytate has also been found to substantially reduce the likelihood of stone formation.[47,54]

Magnesium complexes with oxalate, thereby potentially reducing oxalate absorption in the gastrointestinal (GI) tract and decreasing calcium oxalate supersaturation in the urine. Low magnesium levels are found in up to 18 of the stone formers.[55] In prospective observational studies, higher dietary magnesium is associated with a 30% lower risk of stone formation in men,[48] but not in women.[40,47]

Vitamin C can be metabolized to oxalate and higher vitamin C intake can increase the risk of calcium oxalate stone formation.[56] An observational study in men has found that those who consume 1000 mg or more per day of vitamin C have a 40% higher risk of stone formation compared to men who consume less than 90 mg / day, after accounting for dietary potassium intake.[48] However, the study by Curhan *et al*., does not support an association between the intake of vitamin C and kidney stones.[57]

Vitamin B6 is a cofactor in oxalate metabolism, and vitamin B6 deficiency increases oxalate production and urine oxalate excretion. Observational data have shown that a high intake of vitamin B6 may reduce the risk of kidney stone formation in women,[58] but not in men.[57]

Inadequate fluid intake leading to low urine volume less than one liter per day may be seen in 12 – 25% of first-time stone formers.[59] A randomized trial confirmed the value of increasing the urine volume.[60] Observational studies have found that coffee, tea, beer, and wine are associated with a reduced risk of stone formation.[61,62] Citrus juices can reduce the risk of stone formation,[63] and grapefruit juice intake is associated with a higher risk.[60]

Urinary factors

Abnormal levels of several substances in the urine have been implicated in the pathogenesis of urolithiasis.

Hypercalciuria — Idiopathic hypercalciuriais is the most common metabolic abnormality in patients with calcium-related kidney stones, seen in up to 40% of the patients with calcium stone disease.[64] It is defined as 24 hours of urinary calcium more than 300 mg in males and 250 mg in females.[65] Other common causes of hypercalciuria include hyperparathyroidism and granulomatous diseases.

Hyperoxaluria (urinary oxalate excretion > 45 mg / d) may be present in up to 40% of the male stone formers and in up to 10% of then female stone formers. Although the mean urinary oxalate levels may not differ between cases and controls, the oxalate does appear to be an important independent risk factor for stone formation.[59] Primary hyperoxaluria is a hereditary condition that is associated with stone disease. Enteric hyperoxaluria can also occur for many different reasons, but malabsorption and malnutrition are the most common causes.

Hyperuricosuria (> 800 mg in men and > 750 mg in women per day) is present in up to 35% of the metabolic evaluations, although it is also coexistent with other abnormalities. Up to 20% of these patients will have calcium oxalate calculi.[66] In NHANES III, the prevalence of previous kidney stones in subjects with reported gout was 13.9%.[23]

Hypocitraturia (< 450 mg in men, < 550 mg in women per day) is present in over 30% of the stone patients. In 50% of the cases it coexists with other metabolic abnormalities and in up to 10% of the cases it exists alone.[67] Citrate is protective against stone formation because it forms soluble complexes with calcium, which inhibit crystal nucleation and growth.[68,69] Hypocitraturia is often idiopathic, although other disease states, such as, distal renal tubular acidosis (RTA), hypokalemia, chronic

diarrhea, urinary tract infection, thiazide medication, and a low-alkali, high-protein diet can induce this disorder.[70]

Urine pH — An abnormal urinary pH is another risk factor for nephrolithiasis. High urinary pH leads to increased saturation of calcium phosphate predisposing to nephrolithiasis.[71] Also high urinary pH can lead to the formation of struvite stones due to a low solubility of phosphate, when there is excessive ammonia production by urea splitting organisms.[72] However, a low urinary pH predisposes to uric acid nephrolithiasis.[73]

Pathogenesis of Stone Formation

Kidney stones form when the urine becomes oversaturated with respect to the specific components of the stone.[74] Saturation is dependent on chemical free ion activities of the stone constituents, which are affected by urinary ion concentration, pH, and combination with other substances. Low urinary pH increases the free ion activity of uric acid ions,[73] but decreases the activity of calcium and phosphate ions.[71] Citrate combines with calcium ions to form soluble complexes and can thereby decrease their free ion activity.[68,69]

Although formation of stones can occur through either homogeneous or heterogeneous nucleation, heterogeneous nucleation on a pre-existing surface, such as, cellular debris or another crystal is more common.[75]

The crystals must then aggregate into clinically significant stones. For stone formation to occur before the crystals are eliminated, the crystals anchor at the renal papillae, over areas of interstitial calcium phosphate, in the form of apatite, termed Randall's plaques.[74,76,77] The apatite crystals form in the interstitium around the thin limbs of the loop of Henle.[76] A combination of the apatite crystal and organic material extends from the loop of the Henle tubular basement membrane to the papillary uroepithelial surface, where calcium oxalate crystals or other crystals can adhere and form stones.

Several endogenously produced substances such as uropontin, pyrophosphate, and nephrocalcin have been shown to inhibit calcium crystallization. Differences in the concentration or activity of these inhibitors might account for the differing risk of stone formation among people with similar degrees of urinary oversaturation.[78]

Evaluation of Patient with Nephrolithiasis

Radiological evaluation

Various imaging modalities are available for the diagnosis of urolithiasis. They can also help determine the location and extent of the stone burden and might elucidate the genitourinary abnormalities contributing to stone formation.

A plain radiograph of the abdomen that includes the kidneys, ureter, and bladder (KUB) is a cheap and readily available tool. The sensitivity and specificity of plain abdominal radiography are 58% and 69%.[79]

The renal ultrasound is a useful test for patients who must avoid exposure to radiation or contrast, such as pregnant women and children. Ultrasound can detect calculi in 93% of the patients, but detect all stones in only 60% of the patients. An ultrasound can miss 30% of papillary-calyceal stones.[80] Another study showed a poor sensitivity of 24% and specificity of 90% with the ultrasound.[81] Visualization of the ureteral stones is poor with ultrasound (19%).[82]

Intravenous urography (IVU) is useful in detecting certain genitourinary abnormalities that can predispose to nephrolithiasis, such as, pelvicaliceal abnormalities that cannot be visualized adequately with ultrasonography.[83] Another advantage of an intravenous pyelogram (IVP) is that the osmotic diuresis generated by the contrast agent administered may flush out the offending stone during an episode of acute renal colic. A major disadvantage of IVP is exposure to radiographic contrast material.

A helical CT has a high sensitivity of 97% and specificity of 96% for detecting genitourinary calculi.[84] It has proved to be more effective than IVU in detecting urolithiasis.[85] The sensitivity for detecting ureteral stone is 98.5% for unenhanced CT and 59.1% for IVU. The helical CT takes less time to perform, 30 minutes, including time for curved, multiplanar, reformatted, reconstruction, compared to an average of 108 minutes for an IVU.[86] However, because of a higher radiation dose and cost, some authors recommend that it should be reserved for cases where ultrasonography and IVU cannot visualize the calculi.[82] Scout CT has been shown to be inferior to plain radiography by some authors.[87-89]

Metabolic evaluation of stone formers

Although it is uniformly accepted that patients with multiple stones merit a thorough investigation into the cause of nephrolithiasis, evaluation of the patient with a single stone is controversial. The National Institutes of Health Panels determined that all patients, even those with a single stone, should undergo at least a basic evaluation in order to rule out a systemic etiological mechanism.[90] Patients less than 25 years of age or those with multiple stones, bilateral stones, uric acid stones, staghorn

calculi, nephrocalcinosis, a single kidney or a history of recurrent stones, undergoing workup as a kidney donor or renal impairment should undergo detailed metabolic screening.[91] The relevant tests are included in Box 2, and discussed in more detail in the underlying text.

The evaluation of the stone former includes a stone history and a thorough review of diet, fluid intake, and lifestyle. The evaluation proceeds with a thorough review of the patient's diet and fluid intake. Particular attention is paid to ingestion of foods high in sodium and the quantity of animal protein consumed.

Stone analysis

Determination of stone composition will facilitate appropriate diagnosis and medical management.[92] Patients with uric acid and cystine stones often have higher recurrence than patients with calcium stones,[93] therefore, stone analysis may make it possible to inhibit residual stone growth or recurrence.[94] Patients with calcium stones are heterogeneous with regard to metabolic disorders, but there is a significant likelihood of renal tubular acidosis in those with calcium phosphate calculi.[92] X-ray diffraction, infrared spectroscopy, and polarization microscopy are common techniques for stone analysis. Dual-energy multidetector CT may also be used.[95]

Blood tests

Blood screening tests should be a routine component of the diagnostic evaluation for all stone formers. Serum electrolyte, calcium, carbon dioxide, uric acid measurements as well as measurement of serum creatinine should be obtained, to assess the renal function. These tests are generally inexpensive, and will effectively screen for metabolic abnormalities that may contribute to recurrent stone formation.

Primary hyperparathyroidism may manifest with hypercalcemia. This disorder can be confirmed by determining the patient's serum parathyroid hormone level and serum phosphorous, as an elevated parathyroid hormone level and depressed phosphorous supports the diagnosis. Ionized calcium values must be evaluated if serum albumin levels are abnormal. Moreover, if the diagnosis is suspected, but the calcium level is normal, the administration of a short course of a thiazide-type diuretic can 'unmask' occult cases with resultant hypercalcemia.[96]

Box 2: Diagnostic evaluation for nephrolithiasis

- Stone analysis
- Blood test
  - ❑ Bone Mineral Chemistry, that is, serum calcium, phosphorus, alkaline phosphatase, albumin, parathyroid hormone
  - ❑ Renal tubular functions, that is, electrolytes such as sodium, potassium , chloride
  - ❑ Blood gas analysis
- Urine test
  - ❑ Urine pH
  - ❑ Urine sediment for graveluria
  - ❑ pus cells, RBC
  - ❑ Urine C / S where indicated
  - ❑ 24-hour urine for calcium, phosphate, uric acid, sodium, citrate, oxalate, cystine (if cystinuria is suspected)

Distal renal tubular acidosis may be suspected in the setting of low potassium and carbon dioxide values. Patients with distal RTA generally form calcium phosphate stones.[97]

Less-commonly encountered conditions may require alternative blood tests for diagnosis. Elevated serum oxalate levels and vitamin D levels can diagnose primary hyperoxaluria and hypervitaminosis D, respectively.

Urine tests

A simple clean catch urinalysis can be very informative and should be performed for all stone formers. The specific gravity of urine reflects the general state of hydration of a patient; chronically volume-depleted patients will demonstrate an elevated specific gravity, thereby implying an elevated stone risk. Microscopic examination of the urine sediment can identify crystals that can predict the stone composition. A simple urinalysis will also measure urinary pH. There is a significant variability between fasting urine and 24 hours urine, and 24 hours collection is favored.[98]

Infection is supported with the concomitant presence of pus cells, nitrites, leukocyte esterase, and bacteria. Urine culture can demonstrate the presence of a urea-splitting organisms, such as *Proteus, Pseudomonas* or *Klebsiella,* all of which may be associated with the formation of struvite calculi.[99]

The 24-hour urine collection test is the mainstay of the comprehensive metabolic evaluation. A commonly encountered concern when performing a 24-hour urine study is whether one or two collections should be performed. Pak *et al*., have recommended a single 24-hour collection, as it is more convenient for the patient. They reported a high reproducibility of stone risk factors in repeated samples.[100] However, Parks *et al*., compared two separate 24-hour urine collections and found disparities in around 70% of the patients.[101]

Any urinary tract infection should be treated prior to collection, as it could induce hypocitraturia and an elevated urinary pH, potentially confounding the test results. In general, a 24-hour urine collection should not be performed in the course of an acute stone event, as the patient's

routine lifestyle and dietary habits are altered.[66] Decisions regarding the management of medical therapy during the 24-hour urine collection should be patient- and drug-specific.[64,66]

Conclusion

Nephrolithiasis is a common medical problem worldwide with a significant social and financial burden. The recurrence of this disease is high, so appropriate metabolic evaluation of stone formers is warranted in certain situations. A complete endocrine and metabolic workup is necessary in order to provide appropriate medical treatment.

References

1. Johnson CM, Wilson DM, O'Fallon WM, Malek RS, Kurland LT. Renal stone epidemiology: A 25 year study in Rochester, Minnesota. Kidney Int 1979;16:624-31.
2. Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC. Time trends in reported prevalence of kidney stones in the United States: 1976-1994. Kidney Int 2003;63:1817-23.
3. Nowfar S, Palazzi-Churas K, Chang DC, Sur RL. The relationship of obesity and gender prevalence changes in United States inpatient nephrolithiasis. Urology 2011;78:1029-33.
4. Scales CD Jr, Curtis LH, Norris RD, Springhart WP, Sur RL, Schulman KA, *et al*. Changing gender prevalence of stone disease. J Urol 2007;177:979-82.
5. Odvina CV, Pak CY. Medical evaluation of stone disease. In: Stoller ML, Men MV, editors. Urinary Stone Disease: A Practical Guide to Medical and Surgical Management (Current Clinical Urology, Vol. 1). Totowa, NJ: Humana Press Inc.; 2007.
6. Prezioso D, Di Martino M, Galasso R, Iapicca G. Laboratory assessment. Urol Int 2007;79 Suppl 1:S20-5.
7. Ounissi M, Gargueh T, Mahfoudhi M, Boubaker K, Hedri H, Goucha R, *et al*. Nephrolithiasis-induced end stage renal disease. Int J Nephrol Renovasc Dis 2010;3:21-6.
8. Jungers P, Choukroun G, Robino C, Massy ZA, Taupin P, Labrunie M, *et al*. Epidemiology of end-stage renal disease in the Ile-de-France area: A prospective study in 1998. Nephrol Dial Transplant 2000;15:2000-6.
9. Jungers P, Joly D, Barbey F, Choukroun G, Daudon M. ESRD caused by nephrolithiasis: Prevalence, mechanisms and prevention. Am J Kidney Dis 2004;44:799-805.
10. Soucie JM, Thun MJ, Coates RJ, McClellan W, Austin H. Demographic and geographic variability of kidney stones in the United States. Kidney Int 1994;46:893-9.
11. Maloney ME, Springhart WP, Ekeruo WO, Young MD, Enemchukwu CU, Preminger GM. Ethnic background has minimal impact on the etiology of nephrolithiasis. J Urol 2005;173:2001-4.
12. Maalouf NM, Cameron MA, Moe OW, Sakhaee K. Novel insight into the pathogenesis of uric acid nephrolithiasis. Curr Opin Nephrol Hypertens 2004;13:181-9.
13. Bushinsky DA. Renal lithiasis. Kelly's Textbook of Medicine. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 1243-8.
14. Pundir CS, Goyal L, Thakur M, Kuchhal NK, Bhargava AK, Yadav SP. Chemical analysis of urinary calculi in Haryana. Indian J Med Sci 1998;52:16-21.
15. Ahlawat R, Goel MC, Elhence A. Upper urinary tract stone analysis using x-ray diffraction: Results from a tertiary referral centre in northern India. Natl Med J India 1996;9:10-2.
16. Jawalekar S, Surve VT, Bhutey AK. The composition and quantitative analysis of urinary calculi in patients with renal calculi. Nepal Med Coll J 2010;12:145-8.
17. Koyuncu HH, Yencilek F, Eryildirim B, Sarica K. Family history in stone disease: How important is it for the onset of the disease and the incidence of recurrence? Urol Res 2010;38:105-9.
18. Curhan G, Willett W, Rimm E, Stampfer M. Family history and risk of kidney stones. J Am Soc Nephrol 1997;8:1568-73.
19. Resnick M, Pridgen DB, Goodman HO. Genetic predisposition to formation of calcium oxalate renal calculi. N Engl J Med 1968;278:1313-8.
20. Gambaro G, Fabris A, Puliatta D. Lithiasis in cystic kidney disease and malformations of the urinary tract. Urol Res 2006;34:102-7.
21. D'Angelo A, Calo L, Cantaro S, Giannini S. Calciotropic hormones and nephrolithiasis. Miner Electrolyte Metab 1997;23:269-72.
22. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. JAMA 2005;293:455-62.
23. Kramer HM, Curhan G. The association between gout and nephrolithiasis: The National Health and Nutrition Examination Survey III, 1988–1994. Am J Kidney Dis 2002;40:37-42.
24. Kramer HJ, Choi HK, Atkinson K, Stampfer M, Curhan GC. The association between gout and nephrolithiasis in men: The Health Professionals' Follow-Up Study. Kidney Int 2003;64:1022-6.
25. Taylor EN, Stampfer MJ, Curhan GC. Diabetes mellitus and the risk of nephrolithiasis. Kidney Int 2005;68:1230-5.
26. Meydan N, Barutca S, Caliskan S, Camsari T. Urinary stone disease in diabetes mellitus. Scand J Urol Nephrol 2003;37:64-70.
27. Sakhaee K, Adams-Huet B, Moe OW, Pak CY. Pathophysiologic basis for normouricosuric uric acid nephrolithiasis. Kidney Int 2002;62:971-9.
28. Abate N, Chandalia M, Cabo-Chan AV Jr, Moe OW, Sakhaee K. The metabolic syndrome and uric acid nephrolithiasis: Novel features of renal manifestation of insulinresistance. Kidney Int 2004;65:386-92.
29. Khatchadourian J, Preminger GM, Whitson PA, Adams-Huet B, Pak CY. Clinical and biochemical presentation of gouty diathesis: Comparison of uric acid versus pure calcium stone formation. J Urol 1995;154:1665-9.
30. Pak CY, Sakhaee K, Peterson RD, Poindexter JR, Frawley WH. Biochemical profile of idiopathic uric acid nephrolithiasis. Kidney Int 2001;60:757-61.
31. Pak CY, Poindexter JR, Peterson RD, Koska J, Sakhaee K. Biochemical distinction between hyperuricosuric calcium urolithiasis and gouty diathesis. Urology 2002;60:789-94.
32. Facchini F, Chen YD, Hollenbeck CB, Reaven GM. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. JAMA 1991;266:3008-11.
33. Galvan QA, Natali A, Baldi S, Frascerra S, Sanna G, Ciociaro D, *et al*. Effect of insulin on uric acid excretion in humans. Am J Physiol 1995;268:E1-5.
34. Ferrannini E, Galvan AQ, Gastaldelli A, Camastra S, Sironi AM, Toschi E, *et al*. Insulin: New roles for an ancient hormone. Eur J Clin Invest 1999;29:842-52.
35. Atan L, Andreoni C, Ortiz V, Silva EK, Pitta R, Atan F, *et al*. High kidney stone risk in men working in steel industry at hot temperatures. Urology 2005;65:858-61.
36. Robertson WG, Peacock M, Hodgkinson A. Dietary changes and the incidence of urinary calculi in the U.K. between 1958 and 1976. J Chronic Dis 1979;32:469-76.
37. Larsson L, Tiselius HG. Hyperoxaluria. Miner Electrolyte Metab 1987;13:242-50.
38. Muldowney FP, Freaney R, Moloney MF. Importance of dietary sodium in the hypercalciuria syndrome. Kidney Int 1982;22:292-6.
39. Lemann J Jr, Piering WF, Lennon EJ. Possible role of carbohydrate-

induced calciuria in calcium oxalate kidney-stone formation. N Engl J Med 1969;280:232-7.
40. Curhan G, Willett W, Speizer F, Spiegelman D, Stampfer M. Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. Ann Intern Med 1997;126:497-504.
41. Taylor EN, Curhan GC. Fructose consumption and the risk of kidney stones. Kidney Int 2008;73:207-12.
42. Singh PP, Barjatiya MK, Dhing S, Bhatnagar R, Kothari S, Dhar V. Evidence suggesting that high intake of fluoride provokes nephrolithiasis in tribal populations. Urol Res 2001;29:238-44.
43. Johansson G, Backman U, Danielson BG, Fellstrom B, Ljunghall S, Wikstrom B. Biochemical and clinical effects of the prophylactic treatment of renal calcium stones with magnesium hydroxide. J Urol 1980;124:770-4.
44. Reungjui S, Prasongwatana V, Premgamone A, Tosukhowong P, Jirakulsomchok S, Sriboonlue P. Magnesium status of patients with renal stones and its effect on urinary citrate excretion. BJU Int 2002;90:635-9.
45. Lemann J Jr, Pleuss JA, Gray RW, Hoffmann RG. Potassium administration reduces and potassium deprivation increases urinary calcium excretion in healthy adults. Kidney Int 1991;39:973-83.
46. Curhan GC, Willett WC, Rimm EB, Stampfer MJ. A prospective study of dietary calcium and othernutrients and the risk of symptomatic kidney stones. N Engl J Med 1993;328:833-8.
47. Curhan GC, Willett WC, Knight EL, Stampfer MJ. Dietary factors and the risk of incident kidney stones in younger women (Nurses' Health Study II). Arch Intern Med 2004;164:885-91.
48. Taylor EN, Stampfer MJ, Curhan GC. Dietary factors and the risk of incident kidney stones in men: New insights after 14 years of follow-up. J Am Soc Nephrol 2004;15:3225-32.
49. Bataille P, Charransol G, Gregoire I, Daigre JL, Coevoet B, Makdassi R, *et al*. Effect of calcium restriction on renal excretion of oxalate and the probability of stones in the various pathophysiological groups with calcium stones. J Urol 1983;130:218-23.
50. Borghi L, Schianchi T, Meschi T, Guerra A, Allegri F, Maggiore U, *et al*. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. N Engl J Med 2002;346:77-84.
51. Holmes RP, Assimos DG. The impact of dietary oxalate on kidney stone formation. Urol Res 2004;32:311-6.
52. Breslau N, Brinkely L, Hill K, Pak C. Relationship of animal protein-rich diet to kidney stone formation and calcium metabolism. J Clin Endocrinol Metab 1988;66:140-6.
53. Yachantha C, Hossain RZ, Yamakawa K, Sugaya K, Tosukhowong P, Ogawa Y, *et al*. Effect of potassium depletion on urinary stone risk factors in Wistar rats. Urol Res 2009;37:311-6.
54. Grases F, Isern B, Sanchis P, Perello J, Torres JJ, Costa-Bauza A. Phytate acts as an inhibitor in formation of renal calculi. Front Biosci 2007;12:2580-7.
55. Siener R, Schade N, Nicolay C, von Unruh GE, Hesse A. The efficacy of dietary intervention on urinary risk factors for stone formation in recurrent calcium oxalate stone patients. J Urol 2005;173:1601-5.
56. Baxmann AC, De OG, Mendonca C, Heilberg IP. Effect of vitamin C supplements on urinary oxalate and pH in calcium stone-forming patients. Kidney Int 2003;63:1066-71.
57. Curhan GC, Willett WC, Rimm EB, Stampfer MJ. A prospective study of the intake of vitamins C and B6, and the risk of kidney stones in men. J Urol 1996;155:1847-51.
58. Curhan GC, Willett WC, Speizer FE, Stampfer MJ. Intake of vitamins B6 and C and the risk of kidney stones in women. J Am Soc Nephrol 1999;10:840-5.
59. Curhan GC, Willett WC, Speizer FE, Stampfer MJ. Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. Kidney Int 2001;59:2290-8.
60. Borghi 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.
61. Curhan GC, Willett WC, Rimm EB, Spiegelman D, Stampfer MJ. Prospective study of beverage use and the risk of kidney stones. Am J Epidemiol 1996;143:240-7.
62. Curhan GC, Willett WC, Speizer FE, Stampfer MJ. Beverage use and risk for kidney stones in women. Ann Intern Med 1998;128:534-40.
63. Wabner C, Pak C. Effect of orange juice consumption on urinary stone risk factors. J Urol 1993;149:1405-9.
64. Levy FL, Adams-Huet B, Pak CY. Ambulatory evaluation of nephrolithiasis: An update of a 1980 protocol. Am J Med 1995;98: 50-9.
65. Hodgkinson A, Pyrah LN. The urinary excretion of calcium and inorganic phosphate in 344 patients with calcium stone of renal origin. Br J Surg 1958;46:10-8.
66. Same as ref 59Begun FP, Foley WD, Peterson A, White B. Patient evaluation laboratory and imaging studies. Urolithiasis. The Urologic Clinics of North America. Vol. 24. Philadelphia, PA: WB Saunders Company; 1997. p. 97-116.
67. Coe FL, Kavlach AG. Hypercalciuria and hyperuricosuria in patients with calcium nephrolithiasis. N Engl J Med 1974;291:1344.
68. Heilberg IP, Schor N. Renal stone disease: Causes, evaluation, and medical treatment. Arq Bras Endocrinol Metab 2006;50:823-31.
69. Seltzer MA, Low RK, McDonald M, Shami GS, Stoller ML. Dietary manipulation with lemonade to treat hypocitraturic calcium nephrolithiasis. J Urol 1996;156:907-9.
70. Zuckerman JM, Assimos DG. Hypocitraturia: Pathophysiology and medical management. Rev Urol 2009;11:134-44.
71. Pak CY. Physicochemical basis for formation of renal stones of calcium phosphate origin: Calculation of the degree of saturation of urine with respect to brushite. J Clin Invest 1969;48:1914-22.
72. Griffith DP. Struvite stones. Kidney stones. Kidney Int 1978;13:372-82.
73. Pak CY, Sakhaee K, Peterson RD, Poindexter JR, Frawley WH. Biochemical profile of idiopathic uric acid nephrolithiasis. Kidney Int 2001;60:757-61.
74. Coe FL, Evan A, Worcester E. Kidney stone disease. J Clin Invest 2005;115:2598-608.
75. Bushinsky DA, Friedman PA. Calcium nephrolithiasis. In: Rosen CJ, editor. Primer on the metabolic bone diseases and mineral disorders. Washington, DC: American Society for Bone and Mineral Research; 2008. p. 460-4.
76. Evan AP, Lingeman JE, Coe FL, Parks JH, Bledsoe SB, Shao Y, *et al*. Randall plaque of patients with nephrolithiasis begins in the basement membranes of the thin loops of Henle. J Clin Invest 2003;111:607-16.
77. Sayer JA, Carr G, Simmons NL. Nephrocalcinosis: Molecular insights into calcium precipitation within the kidney. Clin Sci 2004;106: 549-61.
78. Mandel N. Mechanism of stone formation. Semin Nephrol 1996;16:364-74.
79. Mutgi A, Williams JW, Nettleman M. Renal colic. Utility of the plain abdominal roentgenogram. Arch Intern Med 1991;151:1589-92.
80. Vrtiska TJ, Hattery RR, Charboneau JW, Smith LH, Williamson B Jr, Brakke DM. Role of ultrasound in medical management of patients with renal stone disease. Urol Radiol 1992;14:131-8.
81. Fowler KA, Locken JA, Duchesne JH, Williamson MR. US for detecting renal calculi with nonenhanced CT as a reference standard. Radiology 2002;222:109-13.
82. Yilmaz S, Sindel T, Arslan G, Ozkaynak C, Karaali K, Kabaalioglu A, *et al*. Renal colic: Comparison of spiral CT, US and IVU in the detection of ureteric calculi. Eur Radiol 1998;8:212-7.
83. Whitefield AH, Whitefield HN. Is there a role for the intravenous urogram in the 21st century? Ann R Coll Surg Engl 2006;88:62-5.

84. Smith RC, Verga M, McCarthy S, Rosenfield AT. Diagnosis of acute flank pain: Value of unenhanced helical CT. AJR Am J Roentgenol 1996;166:97-101.
85. Wong SK, Ng LG, Tan BS, Cheng CW, Chee CT, Chan LP, *et al*. Acute renal colic: Value of unenhanced spiral computed tomography compared with intravenous urography. Ann Acad Med Singapore 2001;30:568-72.
86. Wang JH, Shen SH, Huang SS, Chang CY. Prospective comparison of unenhanced spiral computed tomography and intravenous urography in the evaluation of acute renal colic. J Chin Med Assoc 2008;71:30-6.
87. Jackman SV, Potter SR, Regan F, Jarrett TW. Plain abdominal x-ray versus computerized tomography screening: Sensitivity for stone localization after nonenhanced spiral computerized tomography. J Urol 2000;164:308-10.
88. Ege G, Akman H, Kuzucu K, Yildiz S. Can computed tomography scout radiography replace plain film in the evaluation of patients with acute urinary tract colic? Acta Radiol 2004;45:469-73.
89. Johnston R, Lin A, Du J, Mark S. Comparison of kidney-ureter-bladder abdominal radiography and computed tomography scout films for identifying renal calculi. BJU Int 2009;104:670-3.
90. Consensus conference: Prevention and treatment of kidney stones. JAMA 1988;260:977-81.
91. Johri N, Cooper B, Robertson W, Choong S, Rickards D, Unwin R. An update and practical guide to renal stone management. Nephron Clin Pract 2010;116:c159-71.
92. Kourambas J, Aslan P, Teh CL, Mathias BJ, Preminger GM. Role of stone analysis in metabolic evaluation and medical treatment of nephrolithiasis. J Endourol 2001;15:181-6.
93. Takasaki E. An observation study on the composition and recurrence of urinary calculi. Urol Int 1975;30:228-36.
94. Ljunghall S, Danielson BG. A prospective study of renal stone recurrences. Br J Urol 1984;56:122-4.
95. Hidas G, Eliahou R, Duvdevani M, Coulon P, Lemaitre L, Gofrit ON, *et al*. Determination of renal stone composition with dual-energy CT: *In vivo* analysis and comparison with x-ray diffraction. Radiology 2010;257:394-401.
96. Eisner BH, Ahn J, Stoller ML. Differentiating primary from secondary hyperparathyroidism in stone patients: The ''thiazide challenge''. J Endourol 2009;23:191-2.
97. Evan AP, Lingeman J, Coe F, Shao Y, Miller N, Matlaga B, *et al*. Renal histolopathology of stone-forming patients with distal renal tubular acidosis. Kidney Int 2007;71:795-801.
98. Capolongo G, Sakhaee K, Pak CY, Maalouf NM. Fasting versus 24-h urine pH in the evaluation of nephrolithiasis. Urol Res 2011;39:367-72.
99. Jennis FS, Lavan JN, Neale FC, Posen S. Staghorn calculi of the kidney: Clinical, bacteriological and biochemical features. Br J Urol 1970;42:511-8.
100. Pak CY, Peterson R, Poindexter JR. Adequacy of a single stone risk analysis in the medical evaluation of urolithiasis. J Urol 2001;165:378-81.
101. Parks JH, Goldfisher E, Asplin JR, Coe FL. A single 24-hour urine collection is inadequate for the medical evaluation of nephrolithiasis. J Urol 2002;167:1607-12.

Cite this article as: Ranabir S, Baruah MP, Devi KR. Nephrolithiasis: Endocrine evaluation. Indian J Endocr Metab 2012;16:228-35.
Source of Support: Nil, **Conflict of Interest:** None declared.