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TOPIC PAPER

Metabolic evaluation of urinary lithiasis: what urologists should know and do

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Abstract
Introduction Urolithiasis is a complex medical entity and regroups several different types of stones, each caused by a multitude of dietary imbalances or metabolic anomalies. In order to better assess the stone-forming patient, urologists should be competent in performing a thorough metabolic work-up.
Materials and methods We reviewed the litterature in order to provide an appropriate overview of the various components of the metabolic evaluation, including stone analysis, biochemistry tests, and urine collection.
Conclusion Performing a metabolic evaluation allows precise intervention in order to treat and mainly prevent stone disease.

Keywords Stones · Urolithiasis · Kidney Calculi/*metabolism · Lithiasis/*metabolism · Hypercalciuria

Introduction

For many urologists, metabolic evaluations of patients with stone disease are a source of many worries since interpretation of results can be a strenuous exercise for the unaccustomed surgeon. Many prefer to either refer patients to a nephrologist or even not perform metabolic evaluation at all. However, as other review papers of this special edition of the *World Journal of Urology* on stone disease and management demonstrate, metabolic evaluation is essential for the proper management of patients, not only in order to prevent recurrences, but also because stone disease is often the first sign of a more significant health issue. Following a stone episode, performing a metabolic evaluation might be a great opportunity to recommend much needed diet and lifestyle changes to your patients, who might be more receptive after a painful event.

Many urology associations develop guidelines to assist urologist in performing metabolic evaluations [1–3]. The newly published AUA Guidelines on the medical management of kidney stones illustrate the need for urologists to be involved in the postoperative and follow-up care of their patients with stones.

In this review paper, we will oversee the evidence regarding the value of metabolic evaluation of kidney stones, identify patients who will benefit the most, and propose a logic and simple approach in the interpretation of the metabolic work-up.

Objectives of the metabolic evaluation

Metabolic evaluation aims at identifying potential anomalies responsible for lithogenesis. It can identify stones secondary to a specific pathology, leading to the appropriate treatment, identify risk factors responsible for stone formation, and establish the basis for a preventive intervention.

A thorough metabolic evaluation includes three key steps: the clinical, radiological, and biochemical evaluation.

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Evidence

In order to demonstrate that performing a metabolic work-up is useful, studies need to properly identify an anomaly, propose a valid intervention (either diet or drug), and assess for recurrences. Since many anomalies exist and stones events are infrequent, only rare studies have evaluated the benefits of metabolic intervention [4]. A few trials have shown benefits of a pharmacological approach [5–13]. Diet modification has also been linked to a reduction in stone recurrence in certain patients.[14]

Thus, even though the evidence demonstrating the benefits of metabolic evaluation is quite sparse, its use has been supported by a multitude of experts [1–3]. Identifying significant diseases, such as hyperparathyroidism, renal tubular acidosis (RTA), and malabsorption, is an important justification on its own to perform metabolic evaluation. It might also be cost-effective in a high-risk population [15].

Who should undergo a metabolic evaluation?

Indications to perform a metabolic evaluation are numerous. Experts advocate performing a limited evaluation in every first-time stone formers, since their risk of anomalies on work-up is equivalent to recurrent stone formers [16]. Even though their risk of recurrence is low at short term, it is estimated at 50 % at 10 years [17, 18], up to 60 % of patients with idiopathic calcium stones will have hypercalciuria [19]. Obviously, patients presenting after several stone events would benefit the most from a proper etiological investigation in order to reduce their rate of stone formation.

Patients presenting with any type of complicated stone event would benefit from reducing their risk of another high-risk event. Patients with bilateral stones disease, solitary kidney or other anatomical anomalies, obstructive pyelonephritis, or stone during pregnancy represent complicated stone events.

Patients who already have known metabolic diseases or anomalies predisposing to stone formation, such as renal insufficiency or inflammatory bowel disease, would also benefit from identifying imbalances requiring adjustments of the disease.

Even though calcium and uric acid stones secondary to childhood obesity are increasing, stone-forming children must be investigated because they will have a high proportion of stones secondary to hereditary conditions (e.g., cystinuria) or significant metabolic diseases.

Finally, patients with specific occupations should undergo evaluation to reduce their risk of having a stone event at a critical moment.

Patients presenting with pure struvite stones benefit the less from a metabolic evaluation. They should however have a bacterial evaluation.

Clinical evaluation

A thorough history is essential for any metabolic evaluation of a patient with stone disease. Blood and urine analysis is impossible to interpret correctly without a corresponding history. The aim was to document all stone episodes and identify risk factors or causal conditions present in the patient's medical and family history, drugs medication usage, or dietary habits. More precisely, a personal history of obesity, gout, intestinal problems, vitamin supplementation (C and D), or certain drugs (e.g., acetazolamide) may be linked to specific stone formation.

Diet history is pivotal since an imbalanced or improper diet explains stone disease in the majority of cases [20]. Urologists should question patients regarding types and amount of liquid ingested daily [21, 22] and try to obtain precision as to the amount of salt, dairy products, proteins, oxalates, fructose, and calories consumed daily [22]. Overconsumption but also insufficient intake, such as with calcium [23], may be responsible for the formation of renal stones.

Radiologic evaluation

Non-contrast CT scans or even ultrasound [24] may be adequate to evaluate an acute episode. However, when planning a surgical intervention or when investigating recurrent episodes of kidney stones, a contrast-enhanced CT can be more proper and reveal significant information [3]. WJU revised, first of all, specific characteristics, such as opacity and density, and form can help suspect a specific stone composition. Also, identification of nephrocalcinosis will lead to suspect hyperparathyroidism, hyperoxaluria, or RTA. Radiological evaluation will also reveal anatomical anomalies responsible for or associated with stone disease, either by inducing stasis, facilitating infection or preventing stone expulsion, some of which may be amenable to surgical correction. Sponge kidney is the most frequent one and is defined by the dilatation of precalicial tubules [25]. Other anomalies include horseshoe kidneys, ureteropelvic junction syndrome, or reflux [26]. These anatomical anomalies may promote stones by inducing urinary stasis, but they may also be associated with metabolic discrepancies and warrant urine collection.

Biochemical evaluation

Biochemical metabolic evaluation: when, how, and what?

Patients should be investigated in their usual setting, while on their usual diet and lifestyle, to reflect the conditions of stone formation. Following an acute stone event or intervention, the

Table 1 Simplified and complete metabolic evaluation

	Limited	Complete
Blood	Creatinine	Add
	Urea nitrogen	Glucose
	Sodium	Magnesium
	Potassium	Bicarbonates
	Chloride	Proteins
	Calcium (± albumin)	PTH
	Phosphorus	
	Uric Acid	
	Carbon dioxide	
24-h urine collection	Volume	Add
	Creatinine	Potassium
	Calcium	Phosphorus
	Sodium	Chloride
	Oxalate	Magnesium
	Citrate	Ammonia
	Uric acid	Urea nitrogen
		Cystine (if cystine stone)
Spot morning urine	pH	Add
	Culture	Urine-specific gravity
	Crystalluria	
Stone analysis	Yes	Yes

metabolic evaluation should not be performed immediately. High pressures in the kidney and NSAIDs use result in some tubular modification interfering with calcium reabsorption that may last a few weeks and alter the work-up. Also, the days following a stone event are usually disrupted and do not reflect the patient's usual lifestyle. Waiting 6 to 8 weeks is recommended [27]. However, certain blood tests (e.g., calcium) collected during an acute event are usually reliable.

In the presence of asymptomatic and non-obstructive renal stones, performing the evaluation before any treatment will allow a more reliable evaluation, since it will reflect the exact setting in which the stone was formed.

Some experts recommend obtaining two complete metabolic evaluations, including one on a weekday and the other during the weekend in order to highlight any anomalies [28, 29]. However, a single urine collection performed during the weekend allows the identification of more than 90 % of anomalies [30]. A limited evaluation is usually acceptable after a first stone episode. However, in complex stone cases, a more complete evaluation allows identification of more anomalies and leads to a more specific treatment plan [31] (see Table 1).

Urine culture, urine-specific gravity, and pH as well as crystal analysis are better evaluated on a fresh morning urine sample and should be analyzed separately.

How to interpret the results of a metabolic evaluation (see Table 2).

- Blood Biochemistry
  - Creatinine
    - An elevated creatinine levels without urinary obstruction would mandate a nephrology referral for the investigation of renal insufficiency.
  - Calcemia
    - Hypercalcemia is uncommon, but when present should lead toward significant health issues such as primary hyperparathyroidism, sarcoidosis, excess calcium or vitamin D, bone metastases, tumors, Paget's disease, and other endocrine disorders [32].
  - PTH
    - Should not be part of the routine work-up. Ask for PTH when known hypercalcemia or high suspicion, such as calcium phosphate stones [32].
  - Uric acid
    - High uric acid levels are common among obese patients. It can be associated with gout. Hyperuricemia without gout promotes uric acid stone formation. Both may be associated with metabolic syndrome (co-occurrence of three out of five of the following medical conditions: abdominal (central) obesity, elevated blood pressure, elevated fasting plasma glucose, high serum triglycerides, and low- and high-density cholesterol (HDL) levels) [33–35].
    - Hypouricemia, a rare condition, can result from Fanconi syndrome, other tubular defects, and other rare conditions.
  - Fasting glucose
    - Discovery of a type 2 diabetes after a stone event is mainly associated with metabolic syndrome and requires a multidisciplinary approach. High blood sugar is usually associated with hyperuricemia and uric acid stones.
  - Phosphate
    - A slightly low phosphate level can be seen with calcium stones. However, when associated with high calcium, it suggests hyperparathyroidism. With a normal calcium level, hypophosphatemia, mainly when associated with calcium phosphate stones, suggests a proximal tubulopathy.
  - Acidosis
    - Low bicarbonates or metabolic acidosis is suggestive of renal tubular acidosis and favors stone formation by decreased urinary citrate levels [36].
  - Potassium
    - Hypokalemia is a surrogate for numerous renal problems and requires further nephrology evaluation.

Table 2 Interpretation of results of the metabolic evaluation

Parameters	Anomalies	Causes
Blood		
Calcium	>2.6 mmol/L	Primary hyperparathyroidism
		Sarcoidosis or other granulomatosis
		Thyroid disease
		Paget
		Tumors or metastasis
		High calcium or vitamin D intake
Phosphorus	<0.8 mmol/L	Primary hyperparathyroidism
		Renal leak
Fasting glucose	>6 mmol/L	Diabetes
		Metabolic syndrome
		Myeloproliferative syndromes
Uric acid	>420 umol/L (M)*	Gout
	>360 umon/L (F)*	Metabolic syndrome
24-h urine collection		
Creatinine	<9 (F) or 13 (M)* mmol/days	Inadequate urine collection
	>13 (F) or 18 (M)* mmol/days	
Diuresis	<2–2.5 L	Insufficient dilution of urine
Calcium	>0.1 mmol/kg/days	With normal calcemia:
		High calcium or vitamin D intake
		Enteric
		Resorptive (osteoporosis or immobilization)
		Renal leak
		Drugs (acetazolamide or steroids)
		Sponge kidney
		High sodium or protein intake
		Idiopathic
		Secondary to hypercalcemia
	>3.8 mmol/L	Insufficient dilution of urine
Urea nitrogen	>5.5 mmol/kg/days	High protein intake
Uric acid	>4.8 mmol/L (M)*	Hyperuricemia
	>4.2 mmol/L (F)*	
	>2.5 mmol/L	Insufficient dilution of urine
Sodium	150–200 mmol/days	High salt intake (>9 g/days)
pH (spot urine check)	<5.5	Acidity leads to uric acid stone
	>6.5	Favors brushite stones formation
Oxalate	>0.45 mmol/L/days	High intake
		Vitamin C intake
	>0.3 mmol/L/days	Insufficient dilution of urine
	0.45–1 mmol/L	Intestinal malabsorption
	>1 mmol/days	Primary hyperoxaluria
Citrate	<1.5–2.5 mmol/days	High protein intake
	or	Metabolic acidosis (diarrhea, GI problems)
	citrate/calcium <0.3	Hypokalemia
		Renal tubular acidosis

* *M* male, *F* female

In summary, discrepancies in blood values are usually associated with significant problems and mandate further investigation. Appropriate referral is thus the adequate step to take.

- 24-h Urine Collection
  - Creatinine or was the urine collection well done?
    - Since creatinine production and excretion is constant, total 24-h hour creatinine allows to verify whether the urine collection was well done. A creatinine value outside specific ranges (9 to 15 mmol/L in males and 13 to 18 mmol/L in females) will reveal an inadequate urine collection.
  - Urine volume
    - Diluting solutes in urine is one of the main methods to reduce the risks of stone formation. Patients urinating less than 2–2.5 L/day are at higher risks of lithogenesis, stressing the need for patients to increase their daily water intake.[21]
  - Calcium
    - Hypercalciuria is defined as more than 0.1 mmol/kg/days (average 7 mmol/days for a 70-kg patient). Even more significant then the absolute output of calcium, an elevated concentration of calcium in the urine is a major risk factor for stone formation. Calcium concentration should be kept lower than 3.8 mmol/L to prevent oversaturation, and reduce the risk of lithogenesis and recurrence [37].
    - Hypercalcemia is almost always associated with hypercalciuria.
    - Hypercalciuria with normal calcemia is seen in 30–60 % of patients with calcium stones [19] and can be secondary to high calcium or vitamin D intake, high-protein diet [38], treatment with acetazolamide or steroids, sponge kidneys or may also be idiopathic.
    - A discrepancy between a low-calcium diet and hypercalciuria without another identifiable cause should prompt an investigation for osteoporosis with a bone mineral density evaluation since calcium most probably comes from the bones[39].
  - Sodium
    - High 24-h urinary sodium output (>150–200 mmol/days), without diuretic treatment, is secondary to excessive sodium in the diet (>9 g/days) and is a major contributor of calciuria. Hypercalciuria in the presence of high sodium output should be managed initially with diet modifications.
  - Urea
    - Urea superior to 5,5 mmol/kg/days represents an intake of more than 1 g/kg/days of protein, which is factor implicating in all types of stones formation. Multiplying urinary urea (mmol/days) by 0.21 and dividing by weight (kg) allows calculating protein intake in g/kg/days.
  - Uric acid
    - Elevated urinary uric acid (>4.8 mmol/days for men and >4.2 mmol/days for women) is secondary to excessive protein intake, type 2 diabetes, or other uncommon diseases.[40] High concentration of uric acid (>2.5 mmol/L) secondary to low urine output also favors stone crystallization.
  - Oxalate
    - Normal oxaluria is usually limited to 0.45 mmol/days with a lithogenic risk increasing with a concentration higher than 0.3 mmol/L. Hyperoxaluria is usually seen secondary to the consummation of food containing oxalates (coke, nuts, dark chocolate, rhubarb, spinach…) or excessive vitamin C intake. Major hyperoxaluria (>1 mmol/days) is usually seen with primary hyperoxaluria or malabsorption problems that lead to a decrease in the absorption of calcium by saponification resulting in an increase in the absorption of oxalate [41]. Hyperoxaluria may also result from the absence of an oxalate-degrading bacteria from the intestinal tract, Oxalobacter formigenes, which leads to increased absorption [42].
  - Citrate
    - Citrate is an important lithogenic inhibitor [43]. Low excretion (<1,5 mmol/24 h) favors stone formation. More importantly, a ratio citrate/calcium <0.3 constitutes a high risk for calcium stones. Hypocitraturia is most often idiopathic, but can result from diarrhea, high protein intake, metabolic acidosis, or certain drugs (diuretics or inhibitors of carbonic anhydrase) [36].
  - Phosphorus and Magnesium
    - Anomalies in electrolytes, phosphorus, magnesium, and calcium in both blood and urine leads toward the diagnosis of tubal defects or hereditary diseases. Referral to a nephrologist is essential.
    - Spot Morning Urine
  - pH
    - A pH lower than 5.5 promotes uric acid stones formation and is the main factor responsible for

Table 3 Stone composition and causal conditions

Stone type	Causal conditions
Calcium oxalate monohydrate (whewellite)	Hyperoxaluria
	Sponge kidney
Calcium oxalate dihydrate (weddellite)	Hypercalciuria
Uric acid	Low urine pH
	Metabolic syndrome
	High uric acid output
Calcium phosphate (carbapatite)	Infection
	Hypercalciuria
	Primary hyperparathyroidism
	High urine pH
Calcium phosphate (brushite)	Hypercalciuria
	Primary hyperparathyroidism
	Sponge kidney
Struvite	Urease-producing organism
Cystine	Cystinuria
Proteins	Chronic pyelonephritis
	Drug related
	Blood clot
	Chronic dialysis
Drugs	Specific
Mixed	Various causes

their formation not elevated urinary uric acid levels [44].
    - A pH higher then 6.5 is usually associated with calcium phosphate stones [45].
    - A pH superior to 7 results from the presence of urease-producing organisms.
- Urine-specific gravity
    - Urine-specific gravity superior to 1.020 on a morning urine sample signals excessive concentration of urine at nighttime.
- Urine culture
    - The presence of urease-producing organisms, such as Proteus, suggests the presence of infectious stones.
- Crystal analysis (Crystalluria)
    - When performed in the optimal setting, on fresh urine immediately after collection, crystal analysis may help identify active lithogenesis. However, in the clinical setting, this is rarely possible, and crystal analysis is usually false positive.

Stone analysis

Stone analysis is a mandatory step in the metabolic evaluation of stone disease. Identification of the stone's nature alone can help identify the causal condition on its own [46] (see Table 3). The stone from a first episode should be analyzed, mainly in pediatrics where hereditary conditions are more likely. Analysis of stones on subsequent episodes should also be analyzed because their nature may change following diet modifications and preventive treatments.

Obviously, certain specific types of stones are linked directly to the causal conditions, such as cystine stones, xanthine, 2, 8-dihydroxyadenin, struvite, ammonium urate, or drug stones. Cystine stone formers need to be referred and followed by a kidney stone specialist since their metabolic evaluation and management is more complicated. Others types, like infection and uric acid stones, suggest more straightforward conditions.

Calcium oxalate (CaOx) stones are the most frequent type. However, distinguishing between CaOx monohydrate and dihydrate will help recommend more precise interventions. CaOx monohydrate is usually associated with hyperoxaluria, which results mainly from diet imbalances or lack of hydration. However, CaOx dihydrate is more often associated with hypercalciuria and warrants a proper urine collection to assess the patients [47, 48].

Phosphate calcium may be associated with various causes. In the presence of a brushite stone, hypercalcemia secondary to primary hyperparathyroidism or distal renal tubular acidosis must be considered. Medullary sponge kidney may be suspected [25]. With carbapatite instead of brushite, these diagnoses may be considered but urinary tract infections and renal tubular acidosis are more likely.

Mixed stones are secondary to either combined conditions (e.g., hypercalciuria and hyperoxaluria) or one condition responsible for various types of stones (e.g., hypercalciuria). Furthermore, analysis of stone morphology, mainly identification of the nidus or a Randall's plaque [49], may help narrow the search for a specific cause. If a stone is formed of several layers of various compositions, each layer may reflect changes in the patients' diet, medication, or condition over time. However, an intact stone is needed to allow proper morphology assessment.

Stone analysis and metabolic evaluation do not always correlate perfectly [50], but can help distinguish the main stone types [51]. Repeating both metabolic evaluation and stone analysis may sometimes produce different results.

When to repeat a metabolic evaluation?

No proper literature exists to recommend a specific follow-up schedule. The guidelines available suggest a follow-up evaluation with a 24-hour urine collection yearly, or depending on stone activity, or within a few weeks (4 to 6 weeks) of the initiation of a treatment in order to assess for response [2, 32]. Repeating urine collection over several years is necessary since the metabolic profile of patients changes over time [52]. In an asymptomatic patient, plain

abdominal X-ray or ultrasound can be performed yearly, or at another frequency depending on stone activity, to assess for stone growth or new formation. Stone analysis should be repeated when available.

Conclusion

With this review, we wish to highlight the basic knowledge urologists should have to perform a metabolic evaluation for stone disease, and we propose a logic and easy way to interpret them. Even more, Web-based tools and smartphone applications are nowadays made readily available to assist in the interpretation of metabolic profiles. Urologists should consider metabolic evaluation as a screening tool to identify improper diet and lifestyle habits as well as significant metabolic diseases. By performing this evaluation, urologists are not necessarily responsible for treating the systemic diseases associated with stones, but they can at least identify and refer patients with significant health issues. By performing a metabolic evaluation, urologists offer to their patients a thorough management of their stone disease and their general health.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards The manuscript does not contain clinical studies or patient data.

References

1. Paterson R, Fernandez A, Razvi H, Sutton R (2010) Evaluation and medical management of the kidney stone patient. Can Urol Assoc J 4(6):375–379
2. Pearle MS, Goldfarb DS, Assimos DG, Curhan G, Denu-Ciocca CJ, Matlaga BR, Monga M, Penniston KL, Preminger GM, Turk TM, White JR, American Urological A (2014) Medical management of kidney stones: AUA guideline. J Urol 192(2):316–324. doi:10.1016/j.juro.2014.05.006
3. Türk C, Knoll T, Petrik A, Sarica K, Skolarikos A, Straub M, Seitz C (2014) The updated EAU guidelines on urolithiasis. EAU Guidelines, edition presented at the 29th EAU annual congress, Stockholm
4. Pearle MS, Roehrborn CG, Pak CY (1999) Meta-analysis of randomized trials for medical prevention of calcium oxalate nephrolithiasis. J Endourol 13(9):679–685
5. Borghi L, Meschi T, Guerra A, Novarini A (1993) Randomized prospective study of a nonthiazide diuretic, indapamide, in preventing calcium stone recurrences. J Cardiovasc Pharmacol 22(Suppl 6):S78–S86
6. Ettinger B, Pak CY, Citron JT, Thomas C, Adams-Huet B, Vangessel A (1997) Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. J Urol 158(6):2069–2073
7. Ettinger B, Citron JT, Livermore B, Dolman LI (1988) Chlorthalidone reduces calcium oxalate calculous recurrence but magnesium hydroxide does not. J Urol 139(4):679–684
8. Ettinger B, Tang A, Citron JT, Livermore B, Williams T (1986) Randomized trial of allopurinol in the prevention of calcium oxalate calculi. N Engl J Med 315(22):1386–1389. doi:10.1056/NEJM198611273152204
9. Laerum E, Larsen S (1984) Thiazide prophylaxis of urolithiasis. A double-blind study in general practice. Acta Med Scand 215(4):383–389
10. Barcelo P, Wuhl O, Servitge E, Rousaud A, Pak CY (1993) Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. J Urol 150(6):1761–1764
11. Hofbauer J, Hobarth K, Szabo N, Marberger M (1994) Alkali citrate prophylaxis in idiopathic recurrent calcium oxalate urolithiasis–a prospective randomized study. Br J Urol 73(4):362–365
12. Scholz D, Schwille PO, Sigel A (1982) Double-blind study with thiazide in recurrent calcium lithiasis. J Urol 128(5):903–907
13. Pak CY, Sakhaee K, Fuller C (1986) Successful management of uric acid nephrolithiasis with potassium citrate. Kidney Int 30(3):422–428
14. Pak CY, Odvina CV, Pearle MS, Sakhaee K, Peterson RD, Poindexter JR, Brinkley LJ (2005) Effect of dietary modification on urinary stone risk factors. Kidney Int 68(5):2264–2273. doi:10.1111/j.1523-1755.2005.00685.x
15. Lotan Y, Pearle MS (2011) Cost-effectiveness of primary prevention strategies for nephrolithiasis. J Urol 186(2):550–555. doi:10.1016/j.juro.2011.03.133
16. Eisner BH, Sheth S, Dretler SP, Herrick B, Pais VM Jr (2012) Abnormalities of 24-hour urine composition in first-time and recurrent stone-formers. Urology 80(4):776–779. doi:10.1016/j.urology.2012.06.034
17. Scales CD Jr, Smith AC, Hanley JM, Saigal CS, Urologic Diseases in America P (2012) Prevalence of kidney stones in the United States. Eur Urol 62(1):160–165. doi:10.1016/j.eururo.2012.03.052
18. Trinchieri A, Ostini F, Nespoli R, Rovera F, Montanari E, Zanetti G (1999) A prospective study of recurrence rate and risk factors for recurrence after a first renal stone. J Urol 162(1):27–30. doi:10.1097/00005392-199907000-00007
19. Worcester EM, Coe FL (2008) New insights into the pathogenesis of idiopathic hypercalciuria. Semin Nephrol 28(2):120–132. doi:10.1016/j.semnephrol.2008.01.005
20. Taylor EN, Stampfer MJ, Curhan GC (2004) Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. J Am Soc Nephrol 15(12):3225–3232. doi:10.1097/01.ASN.0000146012.44570.20
21. Borghi L, Meschi T, Amato F, Briganti A, Novarini A, Giannini A (1996) Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospective study. J Urol 155(3):839–843
22. Curhan GC, Willett WC, Rimm EB, Spiegelman D, Stampfer MJ (1996) Prospective study of beverage use and the risk of kidney stones. Am J Epidemiol 143(3):240–247
23. Borghi L, Schianchi T, Meschi T, Guerra A, Allegri F, Maggiore U, Novarini A (2002) Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. N Engl J Med 346(2):77–84. doi:10.1056/NEJMoa010369
24. Smith-Bindman R, Aubin C, Bailitz J, Bengiamin RN, Camargo CA Jr, Corbo J, Dean AJ, Goldstein RB, Griffey RT, Jay GD, Kang TL, Kriesel DR, Ma OJ, Mallin M, Manson W, Melnikow J, Miglioretti DL, Miller SK, Mills LD, Miner JR, Moghadassi M, Noble VE, Press GM, Stoller ML, Valencia VE, Wang J, Wang RC, Cummings SR (2014) Ultrasonography versus computed tomography for suspected nephrolithiasis. N Engl J Med 371(12):1100–1110. doi:10.1056/NEJMoa1404446
25. McPhail EF, Gettman MT, Patterson DE, Rangel LJ, Krambeck AE (2012) Nephrolithiasis in medullary sponge kidney: evaluation of clinical and metabolic features. Urology 79(2):277–281. doi:10.1016/j.urology.2011.07.1414

26. Gambaro G, Fabris A, Puliatta D, Lupo A (2006) Lithiasis in cystic kidney disease and malformations of the urinary tract. Urol Res 34(2):102–107. doi:10.1007/s00240-005-0019-z
27. Norman RW, Bath SS, Robertson WG, Peacock M (1984) When should patients with symptomatic urinary stone disease be evaluated metabolically? J Urol 132(6):1137–1139
28. Nayan M, Elkoushy MA, Andonian S (2012) Variations between two 24-h urine collections in patients presenting to a tertiary stone clinic. Can Urol Assoc J 6(1):30–33. doi:10.5489/cuaj.11131
29. Parks JH, Goldfisher E, Asplin JR, Coe FL (2002) A single 24-h urine collection is inadequate for the medical evaluation of nephrolithiasis. J Urol 167(4):1607–1612
30. Pak CY, Peterson R, Poindexter JR (2001) Adequacy of a single stone risk analysis in the medical evaluation of urolithiasis. J Urol 165(2):378–381. doi:10.1097/00005392-200102000-00006
31. Yagisawa T, Chandhoke PS, Fan J (1999) Comparison of comprehensive and limited metabolic evaluations in the treatment of patients with recurrent calcium urolithiasis. J Urol 161(5):1449–1452
32. Worcester EM, Coe FL (2010) Clinical practice. Calcium kidney stones. N Engl J Med 363(10):954–963. doi:10.1056/NEJMcp1001011
33. Daudon M, Lacour B, Jungers P (2005) High prevalence of uric acid calculi in diabetic stone formers. Nephrol Dial Transplant 20(2):468–469. doi:10.1093/ndt/gfh594
34. Maalouf NM, Sakhaee K, Parks JH, Coe FL, Adams-Huet B, Pak CY (2004) Association of urinary pH with body weight in nephrolithiasis. Kidney Int 65(4):1422–1425. doi:10.1111/j.1523-1755.2004.00522.x
35. Abate N, Chandalia M, Cabo-Chan AV Jr, Moe OW, Sakhaee K (2004) The metabolic syndrome and uric acid nephrolithiasis: novel features of renal manifestation of insulin resistance. Kidney Int 65(2):386–392. doi:10.1111/j.1523-1755.2004.00386.x
36. Hamm LL, Hering-Smith KS (2002) Pathophysiology of hypocitraturic nephrolithiasis. Endocrinol Metab Clin North Am 31(4):885–893, viii
37. Curhan GC, Willett WC, Speizer FE, Stampfer MJ (2001) Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. Kidney Int 59(6):2290–2298. doi:10.1046/j.1523-1755.2001.00746.x
38. Reddy ST, Wang CY, Sakhaee K, Brinkley L, Pak CY (2002) Effect of low-carbohydrate high-protein diets on acid-base balance, stone-forming propensity, and calcium metabolism. Am J Kidney Dis 40(2):265–274. doi:10.1053/ajkd.2002.34504
39. Pacifici R, Rothstein M, Rifas L, Lau KH, Baylink DJ, Avioli LV, Hruska K (1990) Increased monocyte interleukin-1 activity and decreased vertebral bone density in patients with fasting idiopathic hypercalciuria. J Clin Endocrinol Metab 71(1):138–145. doi:10.1210/jcem-71-1-138
40. Yu TF (1978) Nephrolithiasis in patients with gout. Postgrad Med 63(5):164–170
41. Pak CY, Adams-Huet B, Poindexter JR, Pearle MS, Peterson RD, Moe OW (2004) Rapid communication: relative effect of urinary calcium and oxalate on saturation of calcium oxalate. Kidney Int 66(5):2032–2037. doi:10.1111/j.1523-1755.2004.00975.x
42. Kumar R, Mukherjee M, Bhandari M, Kumar A, Sidhu H, Mittal RD (2002) Role of Oxalobacter formigenes in calcium oxalate stone disease: a study from North India. Eur Urol 41(3):318–322
43. Pak CY (1991) Citrate and renal calculi: new insights and future directions. Am J Kidney Dis 17(4):420–425
44. Moe OW, Abate N, Sakhaee K (2002) Pathophysiology of uric acid nephrolithiasis. Endocrinol Metab Clin North Am 31(4):895–914
45. Parks JH, Worcester EM, Coe FL, Evan AP, Lingeman JE (2004) Clinical implications of abundant calcium phosphate in routinely analyzed kidney stones. Kidney Int 66(2):777–785. doi:10.1111/j.1523-1755.2004.00803.x
46. Pak CY, Poindexter JR, Adams-Huet B, Pearle MS (2003) Predictive value of kidney stone composition in the detection of metabolic abnormalities. Am J Med 115(1):26–32
47. Pierratos AE, Khalaff H, Cheng PT, Psihramis K, Jewett MA (1994) Clinical and biochemical differences in patients with pure calcium oxalate monohydrate and calcium oxalate dihydrate kidney stones. J Urol 151(3):571–574
48. Daudon M, Reveillaud RJ (1984) Whewellite and weddellite: toward a different etiopathogenesis. The significance of morphological typing of calculi. Nephrologie 5(5):195–201
49. Kuo RL, Lingeman JE, Evan AP, Paterson RF, Parks JH, Bledsoe SB, Munch LC, Coe FL (2003) Urine calcium and volume predict coverage of renal papilla by Randall's plaque. Kidney Int 64(6):2150–2154. doi:10.1046/j.1523-1755.2003.00316.x
50. Moreira DM, Friedlander JI, Hartman C, Elsamra SE, Smith AD, Okeke Z (2013) Using 24-hour urinalysis to predict stone type. J Urol 190(6):2106–2111. doi:10.1016/j.juro.2013.05.115
51. Torricelli FC, De S, Liu X, Calle J, Gebreselassie S, Monga M (2014) Can 24-hour urine stone risk profiles predict urinary stone composition? J Endourol 28(6):735–738. doi:10.1089/end.2013.0769
52. Friedlander JI, Moreira DM, Hartman C, Elsamra SE, Smith AD, Okeke Z (2014) Age-related changes in 24-hour urine composition must be considered in the medical management of nephrolithiasis. J Endourol 28(7):871–876. doi:10.1089/end.2014.0002