Chapter 3
24-Hour Urine and Serum Tests: When and What?

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Serum and 24-Hour Urine Tests: When and What?

Kidney stone disease is common; recurrence can be estimated at 52 % in 10 years [1]. Both blood and urine tests can be helpful for kidney stone prevention. Deciding when and what to order is often not very clear, and indications for such tests may vary by practice preference in addition to patient variables. This chapter will attempt to provide the reasoning used to guide the ordering of lab tests in the work up of kidney stone disease. As patients are unique, a clinical impression may provide the primary rationale for ordering certain tests. The clinical opinion of the author is expressed in much of this chapter as evidence is insufficient for much of this topic.

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Who Should Get Further Testing After Forming a Kidney Stone?

Primary prevention of kidney stones with conservative measures such as increasing fluid intake may be financially beneficial if applied broadly [2]. However, it may be unreasonable to expect changes at the population level without the motivation of a previous stone event. Currently, tests of patients' blood and urine are offered to patients with multiple stones, recurrent stones, bilateral stones, unique stones, stones large in size, and in stone formers of young age. More simply, a history of anything in addition to a single moderately sized kidney stone warrants further evaluation. Occasionally, some single stone formers receive blood and urine evaluations in order to prevent future kidney stones. With emerging data to support the association of stones with systemic diseases, such as cardiovascular [3] and premature bone loss [4], the urgency of kidney stone management may be changing. At this time, selection of who should receive these tests remains individualized, as testing all patients remains controversial.

Evaluation and management for the patient who has formed a single kidney stone requires justification. It is important to keep in mind that the prevention of kidney stones requires significant patient effort. In the instance of diet, patients may be asked to make changes to their eating habits for the rest of their lives. If a medication is prescribed, it is important for patients to recognize that its use is often not temporary. Typically, medications work best in conjunction with diet changes. A good example is the use of thiazide-type medications for the treatment of hypercalciuria. In this example, if sodium restriction is not practiced the medication's positive effect may be dampened and potassium losses magnified. For this reason, the screening of patients to elicit willingness to make changes in diet or to take medications is useful. The effort required to collect a 24-h urine sample requires some level of motivation and may predict the willingness to make preventive changes. Most patients may not

be able to commit to being willing to make diet changes or take medications unless results of testing demonstrate risk of recurrence. For those who openly state they are not interested in medications or diet manipulations, further testing may not be useful. At that point, education regarding risk of future stones and general recommendations may be given, and patients can undergo testing in the future if interest changes.

What Tests Should Be Ordered?

It has been suggested that ordering all tests on all patients is not the best approach from a cost perspective [5]. However, specific blood and urine tests may lead to correction of underlying conditions predisposing to kidney stones, such as hyperparathyroidism or sarcoidosis. For this reason, determining which tests should be ordered on which patients is critical.

Basic Blood Chemistry

A basic metabolic panel (BMP) including serum bicarbonate and calcium is done on the majority of patients who have an acute stone event. A BMP may be missing at the time of evaluation and should subsequently be obtained on every stone former regardless of interest in making lifestyle changes. At least one BMP should be obtained at a time when acute illness is not present and in conjunction with a 24-h urine test. Further details regarding the utility of blood tests are shown in Table 3.1.

Serum Calcium and Hyperparathyroidism

Hyperparathyroidism is reported to be present in 2–8 % of kidney stone formers [6]. Therefore, those seen in a stone clinic or stone referral center have a higher likelihood of having this glandular disorder, and the degree of suspicion for hyperparathyroidism should be relatively high.

Table 3.1 Specific serum lab tests and their utility.

BMP (basic metabolic panel)	Should include calcium, potassium, bicarbonate, creatinine, sodium and glucose
Serum calcium total/ionized	High in hyperparathyroidism. May be more sensitive while the patient is under the treatment of thiazide-like medications. The upper limit of normal should still be considered high if PTH is not suppressed. Assessment of ionized calcium may help when total calcium is not clearly elevated
Serum glucose	May serve as indicator for further testing to pursue a diagnosis of diabetes, which is associated with lower urine pH and uric acid stones
Serum bicarbonate	May serve as an indicator of systemic acidosis, which is associated with increased stone risk, especially in the setting of a distal RTA
Serum potassium	High levels would prompt follow-up labs if potassium citrate is prescribed, especially if additional hyperkalemia-causing medications are concomitantly prescribed or if chronic kidney disease exists. Low levels would prohibit use of thiazide-like medications until corrected, and will need to be followed closely if prescribed
Serum sodium	Low sodium would prohibit the use of thiazide-type medications
Parathyroid axis (PTH, calcium, 25-OH vitamin D, phosphorus)	Evaluated if serum calcium is >10.0 mg/dL OR if calcium phosphate stones OR if high urine pH and calcium
PTH	Serves as marker of the level of activity of the parathyroid gland. Should be done at the same time as the rest of the PTH axis
Phosphorus	May be low with high 24-h urine excretion in the setting of hyperparathyroidism. Rarely, may represent a primary renal phosphate leak
25-OH vitamin D	Can be useful to completely define findings from the PTH axis as low vitamin D, in association with elevated PTH, may suggest secondary hyperparathyroidism. Also useful to rule out vitamin D intoxication
Additional tests below	
Magnesium	Magnesium replacement is indicated if hypomagnesemia is detected, especially in patients with hypokalemia
Uric acid	Occasionally useful to guide therapy of calcium stones with xanthine oxidase inhibitors in patients with hyperuricosuria. Useful to follow in patients with gout on thiazide medications
1,25 vitamin D	Only if sarcoid, other granulomatous diseases, or malignancies are suspected

Serum calcium evaluation is the simplest way to screen for hyperparathyroidism, but it may not be persistently elevated, and defining the upper limit of abnormal has been difficult. A blatantly high serum calcium (>10.5 mg/dL on most total calcium assays) may prompt immediate testing and diagnosis of hyperparathyroidism. Surgical treatment by removal of the gland(s) may then correct the problem. But serum calcium within normal laboratory ranges should not necessarily rule out further work up. Normal calcium in hyperparathyroidism has been described and is not rare in stone formers. The fact that the patient has already formed a stone should heighten suspicion of abnormal parathyroid activity, and normal serum calcium in this case should not end the evaluation for it.

The Parathyroid Axis

If calcium phosphate is present in at least 5 % of a patient's stone, the parathyroid axis (blood calcium, phosphorus, parathyroid hormone, and 25-OH vitamin D) should be tested, even if serum calcium was previously normal. To evaluate for phosphorus and calcium wasting, fractional excretion of phosphorus and calcium can be checked when the blood tests are being done. These tests may identify patients with elevated urine phosphorus, low serum phosphorus, and relatively normal PTH levels, which would suggest a primary leak of phosphorus at the level of the kidney. A check of 1,25 vitamin D is not needed in the majority of patients. However, if sarcoidosis or malignancy is suspected, this test should be done. Hypophosphatemia may suggest disorders of renal phosphate reabsorption such as mutations in the genes encoding the sodium-phosphate cotransporters.

All patients with serum calcium >10.0 mg/dL should have blood tests to evaluate the parathyroid axis as well as 24-h urine stone risk assessment. Patients nearing 10.0 mg/dL of total calcium may be found to have even higher calcium values with a test of ionized calcium. If it is not revealing, it may need to be repeated if changes in urine, blood, or stone analyses occur.

24-h Urine Tests

Testing for multiple variables in a 24-h urine collection eliminates the guesswork about potential aberrations and usually also provides information about supersaturation. Several commercial laboratories provide risk "profiles" that provide information from a single 24-h urine collection about both stone promoters and inhibitors. In the single stone former with no radiographic evidence of additional stones, it may not be necessary to order a 24-h urine test. However, age and other comorbidities may justify it. Early intervention after an initial stone event may be most effective in preventing recurrence [7]. While a single 24-h urine test is laborsome, there is a >90 % detection rate [8] of treatable abnormalities when 2–3 studies are completed [9]. With only one study, the impact of collection error can be easily overlooked as predicted creatinine may not identify all inaccurate collections. With a second collection that corroborates collection adequacy, we can be more confident of the evaluation. If the 24-h urinary creatinine values differ by more than 30 %, a third collection can help isolate the more accurate studies. As many patients have the 24-h urine test done shortly after stone formation, diet changes may have been made, and the test may not therefore reveal the risk factors present when the stone was formed. For this reason, a second or third test 6–12 months after the stone event may be better reflective of the patient's typical diet. In the instance of only one test being available, diet modifications may be made until confirmatory 24-h urine results are available to support the use of prescription medications.

While lab tests are helpful in ruling out causative diseases such as hyperparathyroidism, they are only a part of the clinical picture. Management should incorporate other factors such as stone burden, frequency, and type, patient age, and comorbidities. Figure 3.1 provides an overview of patient evaluation.

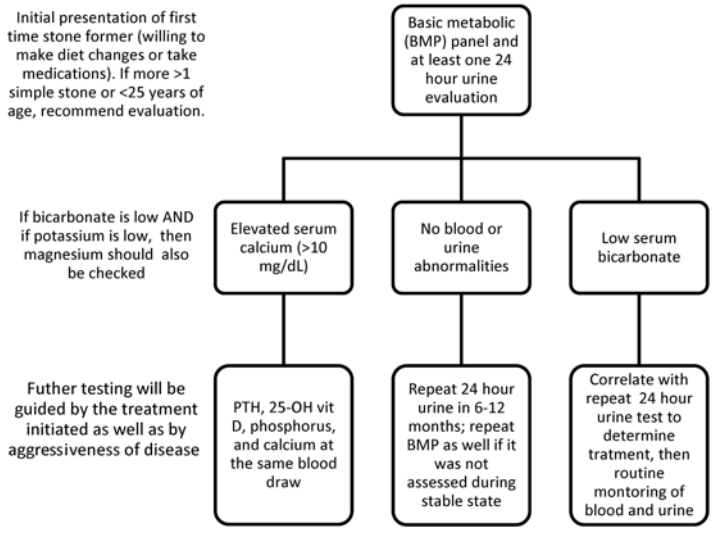

FIG. 3.1. Guidance for targeting the groups of patients that would most benefit from the particular laboratory test.

Am I Missing Something?

In the case of particular diagnoses that are less common, it is important to know when to look further. In addition to hyperparathyroidism and renal tubular acidosis, which are readily treatable, other underlying causes of stones exist. For the most part, younger age in the patient with stones triggers a closer look for underlying disease. Cystine stone formers are typically identified with stone analysis, although the urologist often is aware of the diagnosis based on the physical features of the stone at the time of treatment. Management of cystine stones is significantly different from that of calcium-based stones; cystinuria should therefore be identified for that reason. Cystine screening is a routine part of many but not all 24-h urine evaluations that are geared to kidney stone prevention, but it can also be detected on microscopy or via specifically ordered testing. Genetic

diseases presenting at younger ages with multiple stones, such as primary hyperoxaluria, Lowe's, and Dent's disease, have other characteristic findings that accompany them.

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