Because calcium is required for muscle contraction and nerve signaling, the serum concentration of calcium has obvious significance. Serum calcium also reflects parathyroid hormone (PTH) function and vitamin D status. Although the clinical importance of these 2 hormones and the resulting concentration of calcium in the serum is widely known, the role of urine calcium testing is not often discussed and is less obvious.

The average adult store of calcium is approximately 1-2 kg. The vast majority (99%) resides in the skeleton. Only a fraction of the stored calcium is present in extracellular fluid and available for use in the form of ionized calcium. Ionized calcium is tightly regulated by PTH. Adult calcium plasma concentrations are normally between 8.5-10.5 mg/dL (2.2-2.6 mmol/L). Most of this circulating calcium is bound to albumin. Because of this, changes in serum protein concentrations can affect total blood calcium concentrations. Calcium enters the extracellular fluid through absorption from the gut and resorption from bone. It is removed through secretion into the gastrointestinal tract and urine as well as losses in sweat and deposition in bone.1

The recommended dietary allowance (RDA) for calcium varies with age and, for adults, with gender. Recommended dietary allowance values for adults start at 1000 mg per day. Urine calcium levels will reflect dietary intake. In an average adult urine sample collected over 24 hours, 100-250 mg of calcium (15-20 mmol) is expected. For those on low-calcium diets 50-150 mg/day is expected, while those on a calcium-free diet will have 5-40 mg/day.2 It is also important to note that calcium excretion (CE) is heavily influenced by sodium excretion. Low-sodium diets tend to decrease CE and vice versa.

Although a 24-hour collection is best, random urine calcium measurement can be performed and is expressed in relation to creatinine. A normal reference interval for the urine calcium (mg/dL):urate creatinine (mg/dL) ratio is <0.14. Values exceeding 0.20 are found in patients with hypercalciuria. In children, the calcium:creatinine ratio decreases steadily with time until approximately age 6. It is important to note this fact since most children will be falsely flagged as hypercalciuric using adult cut-offs.

Elevated urine calcium (>300 mg/24 hr) is often a sign of an overactive parathyroid gland. Parathyroid hormone is produced in response to serum calcium levels. Parathyroid calcium-sensing receptors (CASRs) stimulate increased PTH release in the presence of decreased serum calcium levels. Parathyroid hormone then works to increase serum calcium levels. The increases in serum calcium are achieved via increased renal tubule reabsorption of calcium and simultaneous decreases in phosphorus reabsorption. The serum concentration of phosphorus should be very similar to that of calcium since both are held in

Urine Calcium: Laboratory Measurement and Clinical Utility

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Abstract
Urine calcium measurement is a commonly ordered test in clinical laboratories. Unlike other urine markers, the utility of urine calcium is less clear to many laboratorians and physicians. Urine calcium can be used to assess parathyroid disease and familial hypocalciuric hypercalcemia (FHH). Although not predictive of stone formation, urine calcium is frequently elevated in patients with lithiasis. The primary clinical value of urine calcium measurement is to aid in the differential diagnoses of patients and direct optimal treatment options for patients with abnormal serum calcium.

Keywords: calcium, PTH, FHH, hypercalcemia, hypocalcemia, urine, Ca

After reading this article, readers should be aware of the clinical significance of urine calcium testing, including its use and shortcomings in assessment of parathyroid disease; stone formation, and FHH.

Chemistry exam 21001 questions and corresponding answer form are located after this CE Update article on page 687.

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Abbreviations
FHH, familial hypocalciuric hypercalcemia; RDA, recommended dietary allowance; PTH, parathyroid hormone; CaCO₃, calcium carbonate; CaHPO₄ or Ca(H₂PO₄)₂, calcium phosphate; CASR, calcium-sensing receptor; CE, calcium excretion; CR, 24-hour urine calcium/creatinine excretion ratio; CCCR, calcium/creatinine clearance ratio; FEca, fractional excretion of calcium; PH, primary hyperparathyroidism

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equilibrium to each other; as 1 goes up, the other tends to go down. Parathyroid hormone also causes reabsorption of calcium from bone as well as increased synthesis of 1,25-dihydroxy vitamin D, which stimulates calcium absorption from the gut. All of these actions lead to increased serum calcium. Hyperparathyroidism results in excessive uptake and increased concentrations of calcium in serum leading to hypercalcemia and hypophosphatemia. This is then reflected in the urine as hypercalcuria and hyperphosphaturia. Thus, urine calcium levels are often increased in the setting of hyperparathyroidism. However, one-third of hyperparathyroid patients have normal urine calcium, so this test is not reliable in differentiating or diagnosing hyperparathyroidism.²

**Calcium Crystals and Stones**

Calcium is a common ingredient in urine stones and crystals. Calcium oxalate (Ca[CO₃]₂) crystals are the most frequently observed crystals in urine, and 75% of renal calculi have calcium oxalate as a component. Calcium oxalate crystals can form at any pH and have various microscopic morphologies. It is estimated that about half of the oxalate in urine comes from ascorbic acid (vitamin C), which is a precursor to oxalate. Calcium oxalate crystals are also associated with ethylene glycol ingestion, another oxalate precursor. Calcium carbonate (CaCO₃), the main component of marine shells and egg shells, can be found as small granular crystals in alkaline urine. Calcium carbonate crystals are not common in urine but when present can be mistaken for bacteria. To help discriminate these 2, acetic acid can be added to the sample, causing the crystals to release CO₂ which appears as effervescence. Calcium phosphate (CaHPO₄ or Ca[H₂PO₄]₂) crystals can have different morphologies depending on their state of hydration and can be present in the urine sediment of neutral or slightly alkaline or acidic urine. Although not all patients with calcium crystals present in urine will suffer from kidney stones, renal calculi can be caused by calcium oxalate, CaCO₃, or CaHPO₄.

Acidification of urine helps prevent calcium from precipitating as salts and thus prevents falsely decreased measurements of urine calcium. Because of the possible interference of crystals, acidification of urine to pH <2 or pH 4·5 is recommended by many manufacturers of urine calcium reagents. However, adding acid to urine specimens presents some risk to technologists; it will dilute the specimen (although usually only to a minor degree), and it is time-consuming and often requires training and monitoring at collection sites. A recent study has questioned the need to acidify urine.³

**Hypercalciuria**

Any disease causing increases in serum calcium can lead to increases in urine calcium. In addition to hyperparathyroidism, other diseases include multiple myeloma (or any osteolytic neoplasm), osteoporosis, vitamin D overdose, renal tubular acidosis, hyperthyroidism, Paget’s disease, and sarcoidosis. Drugs containing calcium (such as some antacids) and calcium supplements can lead to direct increases in urine calcium. The diuretic spironolactone can also cause increases in urine calcium since it is given as a calcium salt and appears to decrease tubule reabsorption of calcium. Androgens such as nandrolone and treatment with growth hormone can also cause increases in urine calcium. Acetazolamide and systemic corticosteroids are also associated with increased CE.

Patients who have alterations in serum calcium levels are often asymptomatic at the time their abnormal calcium levels are discovered by the clinical laboratory. However, patients with abnormal calcium levels can present with severe signs and symptoms, such as tetany and seizure. Other clinical symptoms suggestive of alteration in calcium metabolism may include peripheral and peripheral paresthesias, carpal and pedal spams, muscle aches, depression, anxiety, fatigue, constipation, abdominal pain, polyuria, and polydypsia. Irritability and lethargy may be the only presenting symptoms in an infant. Maternal hypercalciemia can result in an increased risk of spontaneous abortions, fetal demise, and neonatal hypocalemia. Maternal hypercalciemia can cause neonatal hyperparathyroidism with abnormal serum calcium levels and osteitis fibrosa cystica.⁶ Unrecognized hypoparathyroidism and FHH in women who were diagnosed after the birth of their infants have been reported as well.⁶

Although not ordered on a frequent basis by primary care clinicians, urinary calcium determination may have a significant impact on the diagnosis and treatment of some diseases. In the initial investigation of identifying the cause of abnormal calcium metabolism, a 24-hour urine collection for calcium, urine volume, and creatinine should be performed along with blood testing. The 2 methods most commonly used by clinicians to determine abnormality in renal excretion of calcium are measurement of 24-hour urine calcium or calculation of the 24-hour urine calcium/creatinine excretion ratio (CCCR).⁷ Recent research, however, seems to indicate that these tests may not adequately identify hyperparathyroid patients. Instead, the calculation of the calcium/creatinine clearance ratio (CCCR), also known as the fractional excretion of calcium (FECa), may be a better method by which to identify the cause of abnormal calcium.
metabolism. The CCCR can be calculated from simultaneous determinations of plasma calcium and creatinine along with the 24-hour renal excretions of calcium and creatinine and applying the following formula: (24-hour U-calcium/P-total calcium)/(24-hour U-creatinine/P-creatinine).

A fasting urine calcium may also be useful in uncovering calcium overdose (increased absorption from the gut). If a 2-hour urine collection is obtained after a 14-hour fast, the urine calcium:creatinine ratio should fall to <0.15. If it is >0.15, metabolic/nephrogenic hypercalciuria is suspected.

Use in FHH and Primary Hyperparathyroidism

The prognosis and treatments differ significantly between FHH and primary hyperparathyroidism (PH). Familial hypercalciuric hypercalcemia is typically a benign disease requiring no treatment, whereas surgical intervention is required to treat PH in order to prevent long-term complications of hypercalcemia. Can urine calcium measurement help differentiate PH from FHH? Guidelines have been suggested stating that a CCCR of <0.010 implicates FHH, whereas a CCCR of >0.020 is highly suspicious of PH. Christensen and colleagues compared CCCR measurement with CE and CR in 54 patients with FHH (all with mutations in the CASR gene), and 97 hypercalciemic patients with histological confirmation of PH. They found the CCCR measurement was marginally better than CE or CR at differentiating the 2 diseases. At a cut-off point of <0.020, the CCCR index in their population included 98% of all patients with FHH but still included 35% of patients with PH. Although this cut-off still included some PH patients, the CCCR misclassified fewer PH patients than CR or CE. The authors concluded CCCR might be useful as an initial screening test for FHH, followed by CASR gene analysis for patients <0.020 to rule in/out FHH.

Urinary calcium measurements may also play a role in identifying certain patients with osteoporosis who form kidney stones. Patients at risk for stone formation typically follow different treatment options for their osteoporosis. Giannini and colleagues determined that measuring urinary CE in osteoporotic patients may help identify those patients with idiopathic hypercalciuria and calcium nephrolithiasis. As pointed out in their study, there are data to support the association between low bone density in nephrolithiasic patients with hypercalciuria but not in those without hypercalciuria. More importantly, the authors point out a number of retrospective and prospective studies showing thiazides (which decrease urine calcium), have been associated with a reduction in fracture incidence and an increase in bone density. Giannini and colleagues suggest the majority of the patients in their study may suffer from a diet-independent form of hypercalciuria similar to that seen in patients with kidney stones and low bone density. They conclude that urinary CE should be measured in osteoporotic patients in order to identify this group of patients.

Use in Assessing Stones

In general, patients with calcium urolithiasis excrete more lithogenic substances (calcium and oxalate) in urine than non-stone formers. They also typically secrete less of the stone-inhibitory substances citrate and magnesium. Yet measurement of urine calcium is not considered a good predictive measurement for stone formation. Calcium-based risk markers for urolithiasis have been studied and include ratios such as the calcium/magnesium ratio, the calcium/citrato ratio, and the (calcium/oxalate)/(magnesium/citrate) ratio. Since stone formation is multi-factorial and inherently variable, currently neither calcium nor any other marker for urolithiasis risk is well accepted.

Although urine calcium is not a decisive marker for stone formation, urine calcium measurement may play a role in identifying certain patients who form kidney stones due to the presence of systemic disease (particularly PH). Parks and colleagues compared laboratory features and outcomes of treatment in urinary stone-forming patients with hyperparathyroidism to those without systemic disease. The authors concluded that the hypercalciuria in PH patients who formed stones was greater than the hypercalciuria of the stone-formers without systemic disease. Thus, measurement of the CCCR might help discriminate stone-formers with PH from those with other disorders. This information would be useful in determining appropriate treatment intervention. Interestingly, surgical treatment of the PH did not completely resolve the hypercalciuria or hypophosphatemia in these patients, suggesting the presence of another underlying disorder. This demonstrates the complex nature of calcium homeostasis in that PTH is only 1 of the players involved.

Use in Children

Determining urine CE in children can be a challenge since reference values for the urine/creatinine ratio are not well defined and vary according to diet. Timed 24-hour urine collections can be obtained in older children, but in younger children a random spot urine calcium creatinine ratio repeated on 2-3 occasions at the same time of day is frequently required to assess urine CE. The calcium:creatinine ratio on the second voided urine sample of the day after an overnight fast most closely relates to a 24-hour urine calcium level.

Childhood rickets is an example in which urinary calcium measurements are beneficial. In the diagnosis of rickets, establishing an inappropriately high urinary CE in the face of low serum calcium levels is important. Measuring a urine CR ratio is also part of the initial evaluation in children who have urinary tract calculi as it can help identify metabolic disease if it is present. Hypercalciuria is the most common metabolic cause of stones in Western children and no specific cause is ever determined in a quarter of the cases.

Summary

The major clinical value of urine calcium is to guide the clinician in determining the cause as well as the best treatment options for patients who present with disease related to inappropriate calcium metabolism. The concentration of calcium in urine reflects serum calcium. Many types of urine crystals contain calcium, and random and 24-hour collections are used to assess urine calcium concentration. Primarily, testing is performed to supplement serum testing. No disease is definitively ruled in or out with urine calcium measurement, but the test can be a useful tool when putting together a complete picture of electrolyte homeostasis in the search for a pathology. Urine calcium is often ordered to help assess parathyroid disease and FHH. Although not predictive of stone formation, urine calcium is often elevated in patients with lithiasis.


