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URIC ACID STONES

Uric acid stones account for 5-10% of all those analyzed, although this figure does not take into account passage of smaller fragments and gravel, which commonly occurs in patients with this stone type. The defining feature of uric acid crystallization is its strong pH dependence because the fully protonated form of the uric acid molecule that forms stones and the pK_a of this reaction is approx 5.35 in urine. Therefore, uric acid stones form only when the urine is acidic (pH 5.5 or less), and they often dissolve in vivo when the urine pH is raised to levels that are easily achievable via administration of alkali. For this reason, uric acid stones can often be medically managed, avoiding the need for surgical manipulations or other interventional procedures. In addition, uric acid stones are particularly amenable to medical preventative management.

Uric acid is the major end product of the degradation of the purines adenine and guanine. In humans, purines are derived from diet, *de novo* synthesis, and tissue catabolism. Uric acid is a weak acid with two dissociable protons, with pK_as of 10.3 and 5.57. In human plasma (pH 7.4), most uric acid is present as the monovalent form, and in gouty states it can deposit in tissues as monosodium urate. In human urine, the pK_a is approx 5.3, meaning that when the urine is maximally acidic (pH approx 5.0), the majority of uric acid is in the undissociated form. For example, if a urine sample contains 800 mg of uric acid (a typical quantity), at the acidic pH of 5.0, approx 600 mg will be undissociated uric acid, whereas at a pH of 6.5 only about 100 mg will be in this form. Because it is undissociated uric acid that is relatively insoluble and readily forms crystals and stones, the key role of urinary pH in uric acid stone formation becomes clear. Because a high sodium concentration can increase supersaturation with respect to monosodium urate, which is less soluble than monopotassium urate, and monosodium urate promotes calcium oxalate crystallization, the use of potassium forms of alkali is the preferred treatment strategy.

From the above discussion, it is clear that when the urine is maximally acidic, uric acid stones are most likely to form. Chronic diarrhea (from any cause) or the presence of an ileostomy are potential causes because under these circumstances the kidney must excrete acid to compensate for stool bicarbonate losses. Patients without bowel disease who form uric acid stones appear to have urine that is acidic most of the time. Many appear to excrete inappropriately low amounts of urinary ammonium, and the daily acid load is therefore disproportionately titrated onto phosphate ions, in the process lowering the pH. In this population of uric acid stone-formers, there also appears to be a tendency toward loss of the physiological “alkaline tide” after meals. In older patients in general, there is also a decrease in renal ammoniagenesis, resulting in a more acidic urine and consequent increased risk for uric acid stones. Dietary factors are important in many patients as well because breakdown of ingested proteins contributes to uric acid stone formation in several ways. Animal proteins are high in purines, the precursor of uric acid; glandular proteins such as liver are particularly rich in purines. Urinary uric acid excretion directly correlates with dietary protein ingestion. In addition, animal proteins are rich in sulfur containing amino acids, such as cystine and methionine, which are metabolized to sulfuric acids that must be excreted by the kidney, resulting in an acid urine. Finally, amino acids increase urinary uric acid excretion by inhibiting its tubular reabsorption. The net effect is that a high-protein diet increases the uric acid pool, increases uric acid excretion, and lowers the urine pH, all of which potentiate uric acid stone formation.

The incidence of uric acid stones is higher in patients with gout, perhaps approaching 20%. This combination of uric acid stones and gout has been termed a “gouty diathesis”, and is characterized by a low urinary pH and low fractional excretion of uric acid and high serum uric acid. In this population group, the likelihood of passing a stone correlates with the absolute level of urinary uric acid excretion: those excreting less than 300 mg of uric acid per day had an 11% incidence of stones, whereas those excreting greater than 1000 mg per day had a 50% incidence. Because urinary uric acid excretion correlated with serum uric acid levels, the tendency towards stones also correlated with serum uric acid levels. The gouty population as a group also tends to excrete an overly acid urine, perhaps because of defective renal ammoniagenesis. Therefore, several mechanisms can promote stone formation in these patients. Uric acid stones are also associated with other secondary causes of uric acid overproduction, such as myeloproliferative disorders, a rare genetic disorder of uric acid metabolism (Lesh-Nyhan syndrome), and in association with glycogen storage disease type I in which a chronic acidosis is thought to inhibit reabsorption of uric acid.

Treatment of uric acid stones usually involves drinking water to maintain a dilute urine (ideally >2L/d), a low-protein diet (<1 g/kg of ideal body weight per day), and oral potassium citrate to maintain a urine pH of 6.5-7.0. A higher urinary pH (>7.0) does not increase uric acid solubility further, and may increase the risk of apatite crystallization, which is an important consideration in certain clinical circumstances (e.g., tumor lysis syndrome). The amount of alkali necessary will depend on the diet, but is usually between 50 and 100 mEq/d. Potassium citrate is the preferred salt. It is useful for patients to use pH strips to monitor their urinary pH on treatment, both to achieve the desired pH range and to aid with compliance. Every other day dosing with alkali to raise the urine pH to 7.0 or greater may be an alternative prophylaxis regimen, although it is not recommended for dissolution of stones. This alternate day regimen has the advantage of improved potential for compliance, and patients with large gastrointestinal losses of base (e.g., those with an ileostomy) may be able to achieve an intermittent increase in urine pH better than a prolonged one.

Allopurinol, an inhibitor of xanthine oxidase, an enzyme in the pathway that converts purines to uric acid, is of limited utility for prevention of most pure uric acid stones. Allopurinol is, however, an appropriate therapy for prevention of gout, or in patients with large overproduction of uric acid (e.g., patients with myeloproliferative diseases on chemotherapy). If allopurinol is used, measures to alkalinize the urine are still necessary in most circumstances.

Information taken by permission from: *Essential Urology: A Guide to Clinical Practice*, edited by Jeannette M. Potts, 2004.