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Journal

Journal of Urology, 168(4, Part 1 of 2)

ISSN

0021-0005

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Publication Date

2002-10-01

DOI

10.1097/00005392-200210010-00003

Peer reviewed

Review Article

URIC ACID NEPHROLITHIASIS: CURRENT CONCEPTS AND CONTROVERSIES

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ABSTRACT

Purpose: Uric acid calculi with or without a calcium component comprise a significant proportion of urinary stones. Knowledge of the pathophysiology of stone formation is important to direct medical treatment. The aim of this review is to provide an update on the epidemiology, pathophysiology and management of uric acid renal stones.

Materials and Methods: A MEDLINE search was performed on the topic of uric acid stones. Current literature was reviewed with regard to the epidemiology, pathophysiology, associated medical conditions and management of uric acid stones.

Results: The incidence of uric acid stones varies between countries and accounts for 5% to 40% of all urinary calculi. Hyperuricemia, low urinary output and acidic urine are well known contributing factors. However, the most important factor for uric acid stone formation is persistently acidic urine. Gout and myeloproliferative disorders are associated with uric acid stones. Why most patients with gout present with acidic urine yet only 20% have uric acid stone formation remains unclear. The pathophysiological basis for persistent urine acidity also remains unclear although various mechanisms have been proposed. Urinary alkalization with potassium citrate or sodium bicarbonate is a highly effective treatment, resulting in dissolution of existing stones and prevention of recurrence.

Conclusions: Acidic urine is a prerequisite for uric acid stone formation and growth. Medical management with urinary alkalization for stone dissolution and prevention of recurrence is effective and should be the cornerstone of treatment.

KEY WORDS: uric acid, kidney calculi, urinary calculi, gout

Uric acid is a frequent component of urinary stones and can contribute to calcium oxalate stone formation.¹ Correct diagnosis and understanding of the pathophysiology of uric acid stones have important therapeutic implications. Medical chemolysis is pivotal in the treatment of existing stones. Medical prophylaxis with urinary alkalization and simple dietary modifications is effective and will result in significant cost savings. We review current concepts and controversies regarding the mechanism of uric acid nephrolithiasis and contributing medical conditions. Diagnosis, and medical and surgical treatments are also discussed.

EPIDEMIOLOGY

The prevalence of uric acid stones in the United States is estimated to be 5% to 10%.² Interestingly, these data originate from studies performed more than 30 years ago. Therefore, the current incidence of uric acid stones in the United States may be different. In a more recent study from Veterans Administration hospitals stone analyses revealed that 12% of stones contained some uric acid component and 9.7% comprised pure uric acid.³ Incidence also may vary with age. In 1 study the incidence of uric acid stones was 11% in a geriatric population.⁴ The frequency of uric acid stones also varies in different geographical locations within the United States. In southern states the incidence has been reported at

4% compared with 17% in Chicago.⁵ Other industrialized countries have wide variations in uric acid stone rates, with Germany reporting 17% to 25%, Sweden 4% and Israel up to 40%.^{6–9} Urate stones have frequently been reported in Iran and Pakistan. However, the majority of these stones are ammonium acid urate.¹⁰ These apparent geographical variations indicate that genetic, dietary and environmental factors may have an important role in the formation of uric acid stones.

HISTORICAL REVIEW

Gout is a disease of ancient origin and its association with uric acid stones has long been recognized. Hippocrates described gout in the fifth century BC. In 1683 London physician Thomas Sydenham, who suffered from renal stones, described the clinical features of gout. Michelangelo's special interest in anatomy and kidney function has been ascribed to his own urinary stone disease.¹¹ The artist was diagnosed and treated for urolithiasis by the Paduan physician and anatomist Colombo in 1549. Later in life Michelangelo had gouty arthritis, indicating the likelihood of uric acid stones. This is also reflected in his personal communications in 1549 regarding the special water he was drinking to dissolve the calculi.¹¹

Studies of the composition of urinary calculi were limited before the advent of modern chemistry. Italian anatomist and physiologist Lorenzo Bellini studied the role of water in

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the formation of stones and noted that urinary residues obtained by evaporation could be redissolved in water. This discovery led to the suggestion that urinary stones could be dispersed by increasing urinary flow.¹² Modern chemistry emerged at the end of the 18th century with the discovery of solid matter. Since chemical analysis at that time required large amounts of material, urinary calculi were ideal for this purpose.¹³

In 1776 Carl Wilhelm Scheele described a new substance at the Royal Swedish Academy of Sciences in Stockholm.¹⁴ He found that the main component of a bladder stone being studied was a substance that dissolved in alkali and formed a precipitate in acid solution. Scheele called the substance lithic acid. In an article submitted to the Royal Society in London in 1795 George Pearson, a chemist and physician, described the composition of 300 urinary calculi and suggested that the name of lithic acid be changed to uric acid.¹⁵ He also studied calculi from animals and concluded that, except in man, they never contained uric acid.

URIC ACID METABOLISM

Uric acid is the end product of purine metabolism in humans. In other mammals uric acid is further broken down into allantoin by the enzyme uricase. Allantoin is 10 to 100 times more soluble compared with uric acid. Humans and Dalmatian dogs are the only known mammals prone to uric acid stone formation. However, the mechanism of stone formation in the Dalmatian dog is related to an increased fractional excretion of uric acid.¹⁶

Chemistry of uric acid. Uric acid (2,6,8-trioxypurine) is a weak acid with 2 dissociation constants. Two factors contribute to uric acid solubility: uric acid concentration and solution pH. However, the solubility of uric acid in urine is primarily determined by urinary pH. The first pKa of uric acid is at a pH of 5.5, resulting in the loss of 1 proton from uric acid and the formation of anionic urate.¹⁷ The second pKa is 10.3, which has no physiological significance in hu-

mans. The supersaturation of urine with uric acid occurs when urinary pH is less than 5.5. In contrast, at a pH of more than 6.5 the majority of uric acid is in the form of anionic urate (fig. 1).

The solubility of urate salts is affected by the relative concentrations of cations present in the urine. Increased urinary sodium concentrations promote formation of the monosodium urate complex, which is more soluble than undissociated uric acid. Urine is frequently supersaturated with sodium urate but stones of this type are infrequent. However, supersaturation with sodium urate may contribute to calcium oxalate stone formation via heterogeneous nucleation.

Uric acid pool. Uric acid may be derived by endogenous or exogenous routes. The endogenous production of uric acid from de novo purine synthesis, and tissue catabolism under normal circumstances, is relatively constant at 300 to 400 mg. per day. However, the exogenous pool varies significantly with diet. A diet rich in animal proteins contributes significantly to the purine pool and subsequent uric acid formation by a series of enzymatic reactions involving xanthine oxidase as the final step.

Elimination. Renal excretion is the primary mode of uric acid clearance, accounting for two-thirds of its elimination. Intestine, skin, hair and nails account for the remaining one-third of uric acid excretion. In the intestine bacteria catabolize uric acid into carbon dioxide and ammonia, which are then eliminated as intestinal air or absorbed and excreted in the urine.

Renal handling. Almost all serum uric acid is present in the ionized form, monosodium urate, and only about 5% of urate is protein bound at physiological pH. Urate is filtered completely at the renal glomerulus. However, the normal fractional excretion of uric acid is only 8% to 12%. Therefore, postglomerular resorption and secretion are the ultimate factors regulating the amount of uric acid excretion.^{18,19} The proximal tubule is the site of uric acid resorption and secretion. Almost complete resorption of urate occurs at the S1 segment of the proximal tubule. However, in the S2 segment of the proximal tubule urate is secreted at a rate greater than resorption. Finally, post-secretory resorption occurs at a more distal site of the proximal tubule. Approximately 10% of the filtered urate appears in the urine.

Factors influencing urate excretion. Several factors influence uric acid renal clearance, including intravascular and urinary volume, and plasma urate concentration. Urate resorption in the proximal tubule decreases with increasing extracellular volume. A classic example of the role of extracellular fluid volume in uric acid clearance is the syndrome of inappropriate antidiuretic hormone. In this syndrome the extracellular fluid is expanded, thus, increasing urate clearance and decreasing serum uric acid levels to below normal. Similarly, in pregnancy an increase in urate clearance occurs with increased intravascular volume. In contrast, in diabetes insipidus the extracellular fluid volume is decreased, resulting in an increased uric acid serum level. These observations are of practical value, and indicate that volume expansion is beneficial in uric acid stone formers. Several medications may also influence uric acid excretion.

PATHOPHYSIOLOGY

Composition and different types of uric acid stones. Uric acid stones can be classified based on crystalline composition as anhydrous uric acid, uric acid dihydrate, sodium acid urate monohydrate or ammonium acid urate.²⁰ The anhydrous form is thermodynamically the most stable crystal. The dihydrate form is unstable and undergoes dehydration to the anhydrous form. Uric acid dihydrate has been identified in 20% of uric acid calculi and may represent the entire component. Ammonium acid urate precipitation requires high

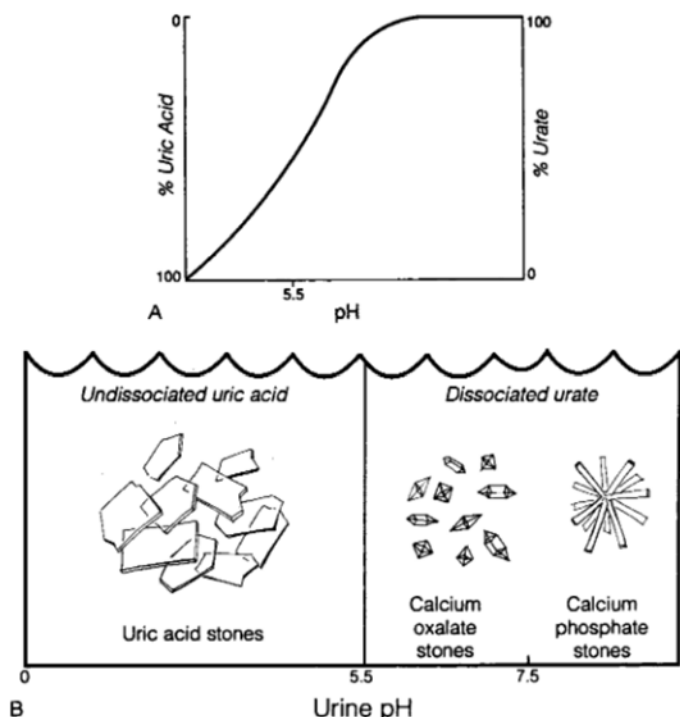


FIG. 1. A, correlation of uric acid solubility with urinary pH. B, characteristic appearance of crystals on urinalysis. Stone type correlates with urinary pH: pH less than 5 is associated with uric acid calculi, while at pH greater than 5.5 undissociated uric acid is replaced with urate, predisposing to calcium stones.

urate and ammonium concentrations and occurs at a higher pH. Recently, a classification of uric acid stones based on their crystalline growth pattern has been suggested.²¹ At present, differences in crystal composition and growth have no clinical implications. However, studies on uric acid crystal growth patterns may provide information on the mechanism of stone formation under various clinical conditions and explain the difference in stone formation rates among patients with similar metabolic abnormalities.

Mechanism of stone formation. Uric acid stone formation requires supersaturation of urinary uric acid. Three factors contribute to the formation of these calculi: acidic urine, hyperuricemia and decreased urinary volume. One or more of these conditions may coexist in a specific patient and contribute to stone disease severity.

Acidic urinary pH. All conditions contributing to acidic urine promote uric acid stone formation. Normal acid-base status is partly maintained by renal acid excretion. Ammonium excretion is the major renal mechanism to correct chronic acid loading. The reported range of urinary pH in normal adults is 4.8 to 7.4 (mean 5.9).²² Urinary pH fluctuates significantly during the day based on diuresis status and diet.^{22,23} A diet high in animal proteins results in higher acid excretion and lower urinary pH compared with a vegetarian diet. Urinary pH is abnormally low in a significant number of patients with gout and in idiopathic uric acid stone formers.^{2,24-26} Although the exact mechanism responsible for acidic urine remains unclear, several hypotheses have been put forth. The concept of a postprandial alkaline tide was proposed more than 150 years ago.²⁷ According to this theory, a postprandial increase in urinary pH is caused by the secretion of bicarbonate from parietal cells of the stomach into the blood in response to luminal proton secretion. The subsequent bicarbonaturia results in an increase in urinary pH. Although an attractive explanation, this mechanism has been questioned by some investigators. In 1 study blockade of gastric acid secretion by histamine-2 blockers did not affect the postprandial alkaline tide.²⁸ Similarly, in a more recent study no correlation was found between postprandial urinary pH and gastric secretion.²⁹

Nevertheless, the presence of an alkaline tide has important clinical implications. In normal individuals the alkaline tide results in dissolution of excreted uric acid and limits or eliminates supersaturation. In contrast, the lack of an alkaline tide has been reported in patients with gout and in idiopathic uric acid stone formers, resulting in supersaturation of urine with uric acid.^{30,31}

A defect in ammonium excretion has been proposed as a mechanism for acidic urine in patients with gout and uric acid stones, who lack the typical response of a postprandial alkaline tide.²⁴ Although some studies have shown decreased ammonium excretion and a low ammonium-to-titratable-acid ratio in patients with gout and idiopathic uric acid stones,^{2,24,30} others have not demonstrated such a difference or have found a difference only under certain dietary conditions.³¹⁻³³ In 1 study there was no difference in renal ammonium excretion and urinary pH between uric acid stone formers and age matched controls, suggesting that lower urinary pH and ammonium excretion may be related to advanced age in patients with uric acid stones.³⁴ In another study no difference in ammonium excretion was found in response to oral ammonium chloride loading between patients with gout and normal subjects.³⁵ These data collectively suggest that the mechanism of acidic urine and lack of diurnal variation in urinary pH in idiopathic uric acid stone formers and gout is multifactorial and needs further investigation.

Hyperuricemia. Hyperuricemia is defined as a mean 24-hour urinary uric acid excretion of more than 600 mg. per day in 2 of 3 collected samples.³⁶ Hyperuricemia may be associated with hyperuricemia, such as in primary gout, or may manifest as an isolated abnormality due to various factors such as diet or

medications. The degree of hyperuricemia correlates with the incidence of uric acid stone formation. In patients with gout the incidence of uric acid stones was 23% in those with urinary uric acid levels less than 600 mg. per day compared with 50% in those with uric acid levels greater than 1,000 mg. per day.²⁴ In another study 11% of patients with uric acid excretion less than 300 mg. per day had uric acid stones.^{37,38} In patients with gout the rate of stone formation is higher when uricosuric drugs are administered.

Dehydration and low urinary volume. All conditions contributing to low urinary output will increase uric acid supersaturation and the risk of uric acid stone formation. A higher risk of uric acid stones has been reported in factory employees working in high temperature surroundings.³⁹ The higher incidence of uric acid stones in Israel may be related to the hot environment.

Hyperuricemic calcium nephrolithiasis and mixed stones. Patients with gouty diathesis may form uric acid and calcium oxalate stones, and in some cases the stones can be mixed in composition. In a recent study similar metabolic abnormalities were identified in patients with gout and either uric acid or calcium stones.⁴⁰ Both groups studied had acidic urine. Gouty arthritis and hyperuricemia were more prevalent in uric acid stone formers. This phenomenon must be differentiated from hyperuricemic calcium nephrolithiasis, which represents a separate entity.⁴¹ By definition, patients with the latter condition present with a urinary pH greater than 5.5 and a 24-hour urinary uric acid level greater than 600 mg.³⁶ Heterogeneous nucleation is the primary mechanism of uric acid induced calcium nephrolithiasis.^{42,43} Adsorption of macromolecular inhibitors of calcium oxalate aggregation is another proposed mechanism.⁴⁴ The primary treatment modality is dietary restriction of purine rich foods. If this approach is unsuccessful, allopurinol is the medication of choice. Potassium citrate is also effective in preventing calcium oxalate crystallization.⁴⁵

Role of matrix and inhibitors of crystallization: a quest for the missing link? Urinary calculi include a crystalline or mineral phase and an organic matrix phase.⁴⁶ Despite decades of investigation, the role of matrix in stone formation and growth remains poorly understood. Matrix is an inhomogeneous material consisting of 64% protein, 12% organic ash, 10% bound water and 5% glucosamine.⁴⁷ Although it was previously believed that matrix composition was constant regardless of crystalline component, recent studies have shown that matrix content varies with stone type. Uric acid stones contain about 2% organic matrix. Abundant acidic amino acids have been found in urinary calculi. In 1 study aspartic and glutamic acid residues were found in 50% and 65% of calcium oxalate and uric acid stones, respectively, compared with 30% of apatite and struvite stones.⁴⁸ Similarly, the content and type of glycosaminoglycans, another component of matrix, differ with stone type.⁴⁹ Hyaluronic acid was found to be the principal glycosaminoglycans in apatite and struvite stones, heparan sulfate in calcium oxalate monohydrate and uric acid stones, and hyaluronic acid and heparan sulfate in calcium oxalate dihydrate stones. Uric acid crystals and stones contain the same organic matrix, and heparan sulfate has been identified almost exclusively in this matrix.⁵⁰ Several proteins have been incorporated into this matrix on a selective basis, 2 of which are albumin and Tamm-Horsfall mucoprotein. The presence and composition of matrix may be a factor contributing to or promoting uric acid stone formation or growth in various clinical settings.

There are no known natural inhibitors of uric acid crystallization. A recent in vitro study demonstrated that mucin and several mucoproteins have an inhibitory effect on uric acid crystallization at supra-physiological levels.⁵¹ The authors concluded that glycosaminoglycans, glycoproteins and surfactant substances may exert protective effects against uric

ASSOCIATED MEDICAL CONDITIONS

acid crystallization. Previous studies have shown low glycoprotein excretion in patients with uric acid stones.⁵² Proteoglycans may enhance urate solubility and decrease tissue deposition of urate crystals in joints and kidneys.⁵³ Interstitial deposits of uric acid and monosodium urate crystals have been reported in 93% of patients with gout.⁵⁴ Although the papillary region of the kidney is generally rich in glycosaminoglycans, altered connective tissue metabolism may result in degradation of the proteoglycans and enhanced interstitial deposition of urate crystals.^{53,55} This hypothesis, based on interstitial deposits of uric acid crystals, is in accordance with the theory of Randall's plaques in the genesis of urinary stones.⁵⁶

CLASSIFICATION

Uric acid stone formers can be broadly divided into 2 general categories: those with and those without an identifiable medical condition contributing to stone formation. Idiopathic or latent gout has been used to describe individuals who have persistently acidic urine as the only identifiable metabolic abnormality.

Idiopathic and inherited uric acid stone formers: separate entities. Idiopathic uric acid stone formers appear to comprise a diverse group. Two studies are frequently cited under this category.^{29,56} In an early study Henneman et al reported the occurrence of uric acid stones in patients without gout or a family history of gout.³⁰ A preponderance of Italian and Jewish individuals was noted. Persistently acidic urine was the only abnormality identified and was attributed to decreased renal ammonium excretion. However, this conclusion was based on ammonium excretion in 4 patients compared with 3 normal controls. Patients with uric acid stones were significantly older, which may explain the differences in ammonium excretion.³⁴ An early study by de Vries et al of Israeli Jews demonstrated an inherited form of uric acid lithiasis in families who presented with severe recurrent stone formation.⁵⁷ The mode of transmission appeared to be autosomal dominant with high penetrance. Persistently acidic urine was noted. These 2 studies likely represent different patient populations and different entities.^{30,57} In the study by Henneman et al³⁰ incidence and patient age were similar to those of patients with gout, while de Vries et al⁵⁷ found that men and women were affected almost equally and onset of stone disease occurred at a younger age.

A more recent study from central Europe demonstrated an idiopathic form of uric acid lithiasis that was not inherited and occurred in 15% of the stone forming population.²⁵ Patients in this study were normouricemic and normouricuric. Although the urine pH was lower compared with controls, no causative role could be identified. Alcohol consumption was higher in the stone formers. The authors suggested that these cases might represent a precursor of gout. However, the exact mechanism of stone formation was unclear.²⁵ It appears that cases of idiopathic uric acid stone formation represent a spectrum, which has been summarized under the term "gouty diathesis."⁵⁸

Pak classified patients with gouty diathesis as having urate overproduction, diminished urate clearance and latent gout.⁵⁸ While the first 2 categories describe individuals who have manifest gout and hyperuricemia, patients with latent gout have a decreased urinary pH as the only abnormality, similar to those described previously as idiopathic uric acid stone formers.² Therefore, the association with gout remains unclear, and the term "gouty" is speculative and is based on the fact that stone disease may manifest before gouty arthritis in up to 40% of patients with gout. Acidic urine is the common denominator in all cases when no associated medical condition is apparent.

Primary gout. The majority of patients with gout present with a tubular defect resulting in decreased uric acid clearance. An increase in de novo synthesis occurs in only about 10% of cases. The biochemical hallmarks of gout include hyperuricemia secondary to increased renal tubular resorption of uric acid, low urinary pH and hypertriglyceridemia. Patients with primary gout may present with arthritic changes and/or urolithiasis. The incidence of uric acid stones in individuals with primary gout is 10% to 20%. The majority of stone formers are men with a mean age in the third decade of life. Acidic urine is present in most patients with gout and it is generally accepted that this is the primary mechanism of uric acid stone formation.⁵⁹

It is unclear why only 10% to 20% of patients with gout have uric acid stones. Intuitively, hyperuricuria increases the risk of stone formation. More than 30 years ago, Yu and Gutman reported this strong association between hyperuricemia and stone formation, noting that 47% of their patients with gout and serum uric acid levels greater than 11 mg/dl formed stones.²⁴ These data suggest that uric acid stones should occur in individuals with gout and severe hyperuricuria. However, in a recent study of patients with gouty diathesis 24-hour uric acid excretion rate was significantly lower in stone formers compared with normal subjects.⁴⁰ This finding is plausible based on the currently accepted pathophysiology of gout, namely the tubular under secretion of uric acid. Hyperuricuria occurs in a relatively small percentage of patients with gout with overproduction of uric acid and an increased urate filtration rate. Therefore, the clinical significance of hyperuricuria in patients with gout and uric acid stones is small. Urinary stones may precede arthritic symptoms in up to 40% of patients, as was likely in the case of Michelangelo.

Myeloproliferative disorders. Myeloproliferative and lymphoproliferative disorders can result in an increased rate of nucleic acid production and turnover with subsequent hyperuricuria. A massive increase in the endogenous purine pool due to tumor necrosis may result in severe hyperuricuria, crystalluria and acute urinary obstruction during chemotherapy for myeloproliferative disorders. In these patients uric acid stone formation incidence is approximately 40%, which is much higher compared to that of patients with gout.²⁴ Benign disorders associated with uric acid calculi include sickle cell disease, hemolytic anemia, thalassemia and polycythemia.⁶⁰

Congenital metabolic enzymatic defects. Several enzymatic defects may result in hyperuricuria and uric acid calculi. Hypoxanthine guanine phosphoribosyl transferase deficiency is a congenital enzymatic defect with complete and partial forms. The complete form occurs only in men and is X-linked. The severe form is known as the Lesch-Nyhan syndrome.⁶¹ Patients with this syndrome present with mental retardation, self-mutilation, gout and uric acid stones. Phosphoribosyl pyrophosphate synthetase overactivity is an X-linked disorder in which hyperuricemia and hyperuricuria are present and uric acid stones may form. Type 1 glycogen storage disease is an autosomal recessive disorder caused by glucose-6-phosphatase deficiency. In addition to hypoglycemia and hyperlactacidemia, patients present with hyperuricemia and hyperuricuria resulting in uric acid calculi.

Inflammatory bowel disease. The reported incidence of urolithiasis in patients with inflammatory bowel disease ranges from 2% to 12%.⁶² These patients may be at increased risk for calcium oxalate and uric acid stone formation. Several factors may affect stone type and severity, including extent of previous small bowel resection and presence of an ileostomy. Uric acid stones have been reported in 50% to 70% of patients with an ileostomy, and calcium stones have been reported in 80% of those with ileal or ileocolic Crohn's disease.⁶³

The predisposition to uric acid calculi appears to be secondary to hypovolemia due to chronic diarrhea or ileostomy fluid loss and chronic intestinal bicarbonate loss, especially in patients with an ileostomy. Hypovolemia can result in metabolic acidosis and a compensatory increase in urinary acid excretion, resulting in acidic urine.⁶⁴ Urinary excretion of uric acid is normal. In contrast, the mechanism of calcium based stone formation is malabsorption induced enteric hyperoxaluria in patients with small bowel disease, dehydration and hypocitraturia due to chronic acidosis.^{65,66}

Diet induced hyperuricuria. A diet high in animal proteins may contribute to hyperuricuria and associated uric acid stones.⁶⁷ Affected patients have normal serum uric acid levels and normal renal clearance of uric acid. The increased protein load induces metabolic acidosis and acidic urine in addition to hyperuricuria, promoting uric acid stone formation.

Renal hypouricemia. Several renal tubular defects such as those found in the Fanconi syndrome, Hartnup disease and Wilson's disease have been associated with hypouricemia and uric acid stones. The mechanism of hyperuricuria has not been clarified. However, a diversion of intestinal uric acid elimination to renal urate excretion has been proposed.⁶⁸ An isolated renal tubular defect of urate handling is an autosomal recessive disease. Affected patients present with urolithiasis and hyperuricuria. A defect in renal tubular resorption with a high fractional excretion of uric acid is the underlying cause.

DIAGNOSIS

Patients with uric acid stones present in a fashion similar to those with other urinary stones. Generally, uric acid stones occur in an older population compared with other stone types.⁴ Medical history can suggest clues in the diagnosis of uric acid stones. Therefore, a detailed medical history is important to identify gout or myeloproliferative disorders.

An acidic urinary pH of less than 5.5 should initiate further evaluation for uric acid calculi. Cystine stones are the only other major stone type associated with acidic urine. Basic laboratory evaluation should include urinalysis, serum electrolytes and uric acid levels. A 24-hour urine collection

should be obtained to evaluate for the presence of hyperuricuria, hypercalciuria, hyperoxaluria and hypocitraturia.

Uric acid stones are relatively radiolucent on routine radiographic imaging. In the past excretory urography, retrograde pyelography and ultrasonography were the modalities used to identify these stones as filling defects and/or hyperechoic foci with typical post-acoustical shadowing. Noncontrast enhanced computerized tomography (CT) is now the best initial modality to image and evaluate urinary stones.⁶⁹ Uric acid stones appear as dense images on CT. Computerized tomography is also useful in differentiating radiolucent calculi from papillary necrosis, transitional cell carcinoma and fungal bezoars. Furthermore, relative CT density can differentiate uric acid stones from other calculi. In a recent study the mean density of 17 uric acid stones (344 ± 152 Hounsfield units) was significantly different compared with 82 calcium oxalate stones (652 ± 490 Hounsfield units).⁷⁰

Other radiolucent stones include matrix, xanthine, hypoxanthine, 2,8-dihydroxyadenine and indinavir stones. Matrix stones are associated with infection and alkaline urine. Xanthine and hypoxanthine calculi are rare stones that occur in patients taking allopurinol. A lack of response to urinary alkalization is another clue suggesting the diagnosis of xanthine and 2,8-dihydroxyadenine stones. Indinavir stones occur in patients with HIV treated with protease inhibitors. Indinavir is the only "radiolucent" stone that does not appear on noncontrast enhanced CT.⁷¹

TREATMENT

Medical therapy for uric acid stones can be divided into 2 categories: urinary alkalization and decreased urinary uric acid. All patients should maintain a 24-hour urinary volume of 1.5 to 2 l.

Urinary alkalization and chemolysis. Urinary alkalization is the cornerstone of medical management of uric acid stones. The concept of uric acid stone dissolution is not new. In 1549 Michelangelo wrote, "We are now certain that I'm suffering from the stone, but it's a small one and thanks to God and to the water I am drinking, it's being dissolved little by little so that I am hopeful of being free of it."¹¹ The water he was referring to, known as Fiuggi water, continues to be mar-



FIG. 2. Right large burden uric acid calculi. Serial CT demonstrates complete dissolution of calculi with oral alkalization during 1-year period.

keted in Italy today and has been reported to dissolve urate stones.

Patients with known uric acid stones without high grade obstruction and infection should receive a trial of oral medical dissolution. We have observed impressive dissolution of large burden uric acid renal stones with oral alkalization (fig. 2). An internal ureteral stent will ensure adequate drainage. Continued alkalization will help prevent future stones.

The goal of urinary alkalization is to achieve a pH of 6 to 6.5.^{72,73} Each patient should be given pH paper to record urinary pH until a steady state is achieved. Administration of alkali should be titrated appropriately. Higher pH values may result in calcium phosphate stone formation and should be avoided. Sodium bicarbonate has been used as a treatment for many years, and has the advantage of being inexpensive and generally well tolerated. The usual dose is 650 mg. 3 times daily.⁶⁰ Commercial baking soda can be used as an alternative, and a dose of 1 to 2 tsp. 3 times daily is generally effective.⁶⁰

A disadvantage of sodium alkali is the increased sodium and fluid load, which can be detrimental in patients with congestive heart failure, liver cirrhosis or hypertension. Furthermore, the sodium load may promote calcium oxalate stone formation by increasing urinary excretion of calcium and sodium. A combination of sodium bicarbonate and acetazolamide (a carbonic anhydrase inhibitor) has been used to improve urinary alkalization with minimal side effects.⁷⁴ Acetazolamide improves urinary alkalization via increased urinary bicarbonate. The induced diuresis prevents sodium and fluid retention. The use of acetazolamide as a solitary agent to produce urinary alkalization is limited. Acetazolamide may increase the risk of calcium phosphate stones by reducing urinary citrate and increasing urinary phosphate excretion. Potassium citrate eliminates the sodium load and is now considered first line treatment for uric acid stone dissolution and prophylaxis. Potassium citrate (30 to 60 mEq. per day) has been reported to increase urinary pH from 5.3 to 6.19 and decreases the risk of uric acid stone formation.⁷⁵

Uric acid stone dissolution by oral alkalization is generally effective, with a reported success rate of 80%. If oral alkalization is ineffective, intravenous alkalization with one-sixth molar sodium lactate is faster and more effective. This solution has the racemic salts of sodium lactate, which are metabolized to bicarbonate in 1 to 2 hours, creating a large acid neutralizing capacity.

Percutaneous or retrograde irrigation of large uric acid stones with alkalizing agents was a common practice in the past. This method was mainly used for dissolution of residual fragments after percutaneous or retrograde manipulation, or in those patients who did not tolerate systemic alkalization. The most commonly used agents were sodium bicarbonate solution (pH 7.0 to 8.0), tromethamine (pH 8.6) and 0.3 M tromethamine E (pH 10.5). These procedures require prolonged hospitalization and are not cost-effective compared with current endourological modalities.⁷⁶

Treatment of hyperuricuria. Hyperuricuria is a risk factor for uric acid stones and may contribute to calcium oxalate stone formation. Purine overconsumption is the most common etiological factor in patients with hyperuricuria. A diet high in red meat, fish and poultry is rich in purines.⁶⁷ Patients with hyperuricuria should ingest a low purine diet. Ingestion of animal proteins also results in increased urine acidity. Urinary urea nitrogen excretion correlates with purine intake and can be used during followup to determine compliance with dietary restrictions.⁷² Patients with symptomatic hyperuricemia or those not responding to dietary modifications should receive allopurinol.

Allopurinol is a xanthine oxidase inhibitor that converts hypoxanthine to xanthine and xanthine to uric acid. Xanthine and hypoxanthine are soluble and are excreted by the

kidney. Allopurinol also decreases de novo purine synthesis. Inhibition of purine synthesis does not occur in patients with myeloproliferative disorders or hypoxanthine guanine phosphoribosyl transferase deficiency. Therefore, xanthine stones may form during allopurinol therapy in these individuals.^{77,78}

Oxypurinol is a metabolite of allopurinol. High dose allopurinol therapy rarely has been associated with oxypurinol stones or nephropathy.⁷⁹ In patients with myeloproliferative disorders allopurinol should be given before chemotherapy to reduce the risk of uric acid stones due to cell lysis.

The usual dose of allopurinol is 300 mg. per day. Dosage should be adjusted in patients with renal insufficiency. Allopurinol is generally well tolerated, with minor side effects that include skin rash and gastrointestinal irritation. Liver function may be altered and increased liver enzymes have been reported requiring followup. However, the most severe side effect is allergic response resulting in hemorrhagic skin lesions and potentially fatal vasculitis (the Stevens-Johnson syndrome). Pruritus precedes the development of skin lesions and patients should be instructed to stop the medication if this occurs.

Surgical management. Principles of surgical treatment for large stones or those not responding to systemic alkalization are identical to those for other stone types. All lithotripsy modalities are effective for uric acid stone fragmentation. Holmium:YAG lithotripsy of uric acid calculi releases cyanide as a thermal breakdown product. However, clinical studies have not demonstrated any toxicity or side effects associated with cyanide production.⁸⁰ Uric acid stones fragment easily with extracorporeal shock wave lithotripsy, and this modality may improve oral chemolysis by increasing the exposed stone surface.⁸¹ Intraoperative stone localization may require placement of localizing catheters with retrograde contrast injection.

CONCLUSIONS

Persistently acidic urine resulting in supersaturation of uric acid is the only metabolic abnormality found in many patients with uric acid stones. Although the mechanism responsible for acidic urine in many patients remains unclear, urinary alkalization is the cornerstone of medical management and should be the primary mode of treatment in the absence of absolute indications for surgical intervention. Furthermore, prophylaxis with urinary alkalization using oral alkali prevents stone recurrence and associated morbidity.

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