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Uric Acid Nephrolithiasis: A Systemic Metabolic Disorder

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Abstract

Uric acid nephrolithiasis is characteristically a manifestation of a systemic metabolic disorder. It has a prevalence of about 10% among all stone formers, the third most common type of kidney stone in the industrialized world. Uric acid stones form primarily due to an unduly acid urine; less deciding factors are hyperuricosuria and a low urine volume. The vast majority of uric acid stone formers have the metabolic syndrome, and not infrequently, clinical gout is present as well. A universal finding is a low baseline urine pH plus insufficient production of urinary ammonium buffer. Persons with gastrointestinal disorders, in particular chronic diarrhea or ostomies, and patients with malignancies with a large tumor mass and high cell turnover comprise a less common but nevertheless important subset. Pure uric acid stones are radiolucent but well visualized on renal ultrasound. A 24 h urine collection for stone risk analysis provides essential insight into the pathophysiology of stone formation and may guide therapy. Management includes a liberal fluid intake and dietary modification. Potassium citrate to alkalinize the urine to a goal pH between 6 and 6.5 is essential, as undissociated uric acid deprotonates into its much more soluble urate form.

Keywords

Uric acid nephrolithiasis; Metabolic syndrome; Gout; Acid urine; Hyperuricosuria; pH; Urine buffer; Ammonium; Alkaline; Potassium citrate

Relationship of Uricotelism and Uric Acid Stones

Purine nucleotide metabolism results in the relatively water-insoluble uric acid in humans. In most mammals, uric acid is an intermediate metabolite, as it undergoes oxidation by hepatic uricase to the more soluble allantoin. However, multiple cumulative mutations result

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in a non-functioning uricase gene in higher primates including humans. The high concentration of uric acid can lead to disease such as gout and uric acid nephrolithiasis. In addition, high uric acid has been postulated to contribute to hypertension, vascular disease, and progression of chronic kidney disease.

Uric acid has a pervasive presence in all body fluids. The serum level of uric acid is determined by its rate of synthesis, rate of excretion by kidneys and gastrointestinal tract, and metabolism (in organisms with uricase). In species such as birds, uric acid is the principal form of nitrogen excretion, termed uricotelism [1, 2]. In such instance, uric acid is a metabolic end product and hence not degraded. One rationale of uricotelism is that uric acid can be excreted in its solid phase that relieves the organism of the burden of contemporaneous water excretion, a distinct advantage for water conservation [3, 4]. The anatomic design of these organisms permits the expulsion of solids in the urine without physical blockage. It would appear that the very purpose of having uric acid in the urine is so that it will precipitate [3, 4].

In contrast, the use of urea as a primary mode of nitrogen excretion, termed ureotelism, carries the burden of some degree of obligatory water excretion as a solvent for the urea despite the high solubility of urea. In general, ureotelic organisms metabolize uric acid to allantoic acid and allantoin, which are much more soluble than uric acid and thus evade the problem of crystallization. There is a seemingly anomalous paradox in higher primates, who are principal ureotelics but have evolved to lose the ability to metabolize uric acid, thus rendering it an end product of metabolism [1, 3, 5, 6]. As a result, higher primates have rather high concentrations of uric acid in the extracellular fluid and urine. While the high uric acid in the extracellular fluid is believed by some to be adaptive, it is difficult to fathom how high urinary uric acid serves any useful purpose. The loss of uricase in humans, chimpanzees, orangutans, and gibbons may have conferred a survival benefit, and thus has been selected for, but exactly how uric acid exerts positive effects in higher primates is still unresolved.

Regardless of how uric acid may bestow an advantage [3], the undeniable fact is that uric acid levels are high. In most mammals, serum levels of uric acid are in the lower micromolar range, typically between 3 and 120 μM (0.05–2.0 mg/dl), but in humans and great apes, they are typically between 200 and 400 μM (about 3.5–7.0 mg/dl). In plasma pH, a uric acid level of 400 μM is still within the safe haven of solubility. However, in the more acidic environment of urine, the situation is drastically different. The low pH places uric acid perpetually in the border of precipitation. Hence, no matter what advantage is gained from the higher plasma uric acid levels, the sacrifice is the risk of urinary precipitation of a substance that is utilized by our avian relatives to excrete nitrogen in a solid phase in the urine. In other words, having urinary features of uricotelism in a ureotelic is by-and-large counterproductive. Can evolution deviate from its fundamental tenet of following positive selective pressures? It is conceivable that urine pH was more alkaline in our primate ancestors when this trait evolved so high urinary uric acid was not a negative trait. It is also possible that uric acid crystallization is not potent enough to exert a negative reproductive effect to shape evolution.

From an evolutionary viewpoint, one can envisage uric acid nephrolithiasis as a result of a trade-off where the advantage gained from higher uric acid levels in the body is attained by the compromise of maintaining a risky substance of borderline solubility in the urinary tract. In the presence of high urinary uric acid, any condition that lowers urine pH in the kidney or bladder will lead to uric acid urolithiasis. We will elaborate on how uric acid nephrolithiasis is a disease of low urinary pH in most, but not all cases.

History and Epidemiology

The oldest documented human urolith was a bladder stone in a boy discovered by British Egyptologist G. Elliot Smith in Upper Egypt in 1901. The mummy is believed to have lived close to 7,000 year ago in pre-dynastic Egypt. The stone had a mixed composition, which included a small amount of uric acid [7]. Both Hippocrates (460–370 B.C.) and Galenus (131–201 A.D.) noted the association of arthritis, gouty tophi, and bladder and kidney stones and proposed a pathogenic relationship of these features [8]. Sydenham (1624–1689), a gout and stone sufferer himself, hypothesized that an increase in a “stone-producing substance” resulted in precipitation in the urinary tract [9].

Uric acid (2,6,8-trioxypurine) was first isolated from bladder stones in 1776 by the Swedish pharmacist Scheele (1742–1786) who also coined the name “lithic acid” to refer to the acidic substance in these calculi [10, 11]. Around the same time, Wollaston (1766–1828) made the seminal identification of cystine stones (named after their bladder locale) [12, 13], which inspired Pearson (1751–1828) [14] to analyze a large number of stones and found Scheele’s lithic acid in all of them. Fourcroy (1736–1802) and Vauquelin (1763–1829) analyzed at least 600 human and animal stones and made similar findings [15]. It was Fourcroy who proposed that the term “uric acid” should replace lithic acid. Finally, the German chemist Fischer (1852–1919) was able to synthesize and elucidate the structures of compounds he termed purines (“purum uricum”) in 1884.

Bladder calculi were a wretched curse in eighteenth-century Europe, as the sole therapy appeared to be surgery with staggeringly high mortality [16]. It is astounding to see that in modern times, uric acid stones are one of easiest renal calculi to dissolve medically. Sir William Osler (1849–1919) stated that uric acid is the most “important substance which may form the renal sand, the small solitary, or the large dendritic stones.” [17].

The history of kidney uric acid stones is more difficult to trace. It is primarily a disease associated with the metabolic syndrome and type II diabetes, as is gout. In England, gout as a disease of the wealthy emerged as an epidemic in the 18th and 19th century. It was associated with a rich diet and excessive alcohol consumption. In the 20th and 21st century, developing nations have seen a sharp increase in gout likely due to a change in diet, as well a higher prevalence of obesity. The same holds true for minority populations in industrialized countries, such as Hispanics.

In the industrialized world, about 10–15% of people will have at least one kidney stone in their lifetime. As the overall prevalence for stone disease has increased so has the frequency of uric acid stones. Among all stone formers, however, the prevalence has remained remarkably stable over the past several decades. In one analysis conducted in the 1960’s,

about 10% of stones were composed of uric acid [18]. A study conducted by the Department of Veterans Affairs in the United States in the 1980's also found an incidence of about 10% [19]. A more recent study from Canada compared stone composition during the early 1980's and late 1990's and found no significant change in the incidence of uric acid stones over almost 20 years [20]. In an analysis of over 224,000 stones from 22 German centers, uric acid comprised 11.7% in males and 7% in female stone formers and has remained steady [21].

Persons older than 65 years of age are twice as likely to develop stones as younger persons [22]. Women have a lower rate of developing kidney stones in general, with a life-time incidence of roughly half that of men. The same applies to uric acid stones where prevalence in women is lower [23]. Ethnicity appears to matter. In certain regions of the Middle East, uric acid stones can be up to a third of urolithiasis [24]. A particularly high incidence of uric acid stones is found among a recent group of immigrants to the United States, the Hmong of Laos. More than 50% of all stones are comprised of uric acid [25]. However, the VA study [19] did not find significant regional variation within the United States. Asian countries in general have a very low rate, for example, less than 1% in India [26], though with some exceptions, such as in Okinawa (Japan), where a prevalence of 15% was reported [27]. Both dietary and genetic factors likely play a role in the geographic variation. Indeed, the development of insulin resistance in obesity, the metabolic syndrome, or overt diabetes mellitus (type 2) are associated with a low urine pH, and thus a much higher risk for uric acid stones [28, 29], as further discussed later under "Pathogenesis".

Pathogenesis of Uric Acid Nephrolithiasis

Physiology of Purines and Uric Acid/Urate

In humans, uric acid is the end product of purine nucleotide metabolism. The formation of uric acid involves purine degradation to inosinic acid and hypoxanthine. The enzyme xanthine oxidase (XO) then converts hypoxanthine to xanthine and uric acid. While this is the final step in higher primates, most mammals are able to convert uric acid to allantoin via uricase. Allantoin is highly soluble without any known adverse effects on health. Recombinant uricase (rasburicase and the more recent pegylated version [30]) is in routine clinical use for situations of anticipated severe hyperuricemia, such as chemotherapy induced tumor lysis syndrome and the prevention of acute crystal-induced uric acid nephropathy [31]. XO inhibitors are effective in reducing new uric acid formation, but accumulation of xanthine may result in acute xanthine nephropathy [32].

The sources of purines include (a) de novo synthesis, (b) cellular RNA from the normal turnover of cells, and (c) exogenous, i.e., dietary sources. Under normal condition, endogenous uric acid production is quite stable at about 300–400 mg per day. The role of exogenous purines is variable though it usually contributes less than 50% of total uric acid production. Rich sources of dietary purines include red meat (especially meat gravies, and organ meat such as liver, heart, kidney), poultry, fish (especially trout, herring, sardines), legumes (especially anchovies, asparagus), and mushroom. In a comparison of a high-purine to a purine-free diet, an increase of 50% or more in urinary uric acid has been observed [33]. On a typical Western diet, humans excrete about 10 mg/kg bodyweight of urates per day

[34]. A purine-rich diet will contribute to hyperuricosuria (defined as daily excretion >800 mg in men and >750 mg in women) but does not invariably produce hyperuricemia (defined as a serum level >7 mg/dl in men, >6 mg/dl in women).

The daily elimination of uric acid is achieved via the gastrointestinal tract (30%) and the kidneys (70%). Unlike that of a classical end product, the renal handling of uric acid is complex and consists of multiple steps. About 90% of uric acid is freely filtered; the remaining 10% are protein-bound urates. The filtered load undergoes several cycles of absorption and secretion for a final fractional excretion rate of about 10% [35]. Several drugs influence renal handling of uric acid. Some have uricosuric properties, such as benzbromarone, indomethacin, losartan, probenecid, and salicylic acid, thus increasing the risk for renal stones. Pyrazinamide is anti-uricosuric and is well known to precipitate gout in some individuals. Recent molecular identification and functional analysis of urate specific transporters have provided important new insight [36–38]. This is of interest not just to better elucidate the complex renal handling of uric acid, but also for our understanding of some rare forms of familial nephrolithiasis associated with hypouricemia due to a high fractional excretion of uric acid (“renal leak”) [39, 40].

Pathophysiology of Uric Acid Stone Formation

This review will focus on pure uric acid stones. The reader is referred to selected literature regarding hyperuricosuric calcium oxalate stones and ammonium urate stones [39, 40]. The biochemical abnormalities in uric acid stone formation are low urine pH, which is by far the most important, followed by high urine uric acid and low volume. The pathophysiology of these primary abnormalities is discussed later and summarized in Fig. 1.

Acid Urine

Urinary pH is the main determinant of uric acid crystallization and precipitation, and in fact, the vast majority of uric acid stones are associated with a low urine pH, rather than excessive urinary concentration of uric acid due to hyperuricosuria and low urine volume. Uric acid nephrolithiasis is a quintessential disease of aciduria [41–44].

Uric acid is a weak organic acid with a pKa_1 of 5.3. Thus, at a physiologic pH of 7.4, virtually all uric acid is in its de-protonated and much more soluble urate form. In urine, however, the pH can vary over a wide range, which determines the concentration of uric acid. The risk of uric acid crystallization increases with a progressive fall in urine pH. At a pH 5.3, 50% of uric acid will be in its poorly soluble form. For example, since the solubility of undissociated uric acid is 97 mg/l, at a pH of 6.5, approximately 1,100 mg of total uric acid per liter or urine needs to be excreted to exceed solubility. This scenario is much less likely then crystallization due to an acid urine pH (Fig. 2). The solubility of de-protonated urate also depends on its cation. Potassium urate is more soluble then sodium urate, which partially contributes to the increases risk of urate-induced calcium lithiasis during treatment with sodium bicarbonate [45].

A rather unique feature of uric acid crystals is the fact that they can dissolve in a more alkaline milieu. It is conceivable that uric acid precipitation in supersaturated and acidic urine is a rather frequent phenomenon, as it may occur after a protein-rich meal. However,

for uric acid crystals to form nuclei, and to subsequently aggregate to form a stone, *persistently* acid urine may be a prerequisite. All individuals exhibit diurnal variations in urine pH [46–49]. Calcium oxalate and mixed calcium oxalate/calcium phosphate stone formers have a low urine pH only in the early morning hours [50]. In comparison, uric acid stone formers exhibit a persistently low urine pH throughout the entire day [51, 52].

The primary driver for uric acid stones is low urine pH. Low urine pH is either due to higher acid production and excretion (endogenously produced or exogenously ingested), an inadequacy of urinary buffers, or both. Even urine at a pH of 5 contains only 10 μmoles of free H^+ per liter—an irrelevant amount of H^+ excretion considering humans normally require acid excretion close to 1 mmole per kg body weight per day. Urinary buffers are foremost the high capacity, high pKa “open” buffer ammonium, the rest comprise the lower capacity, lower pKa, and primarily “closed” buffers, collectively referred to as “titratable acid” [53]. Significant titratable H^+ acceptors include phosphate, creatinine, urate, citrate, and oxalate. While the excretion rate of these buffers do not vary greatly in response to acid–base changes, the quantity of urinary ammonium excretion can be greatly augmented, up to 200 mEq/day in states of severe acidosis. Thus, in the face of increased acid loading, ammonium is the principal urinary buffer, and thus bears the main responsibility for renal elimination of acid.

Uric acid stone formers maintain acid–base parameters in balance and in steady state. Net acid excretion is “normal” from the perspective of external balance. However, three abnormalities contribute to the formation of stones: First, there is an increased acid load imposed on the kidney. This feature is seen in both type 2 diabetics and uric acid stone formers [51, 54–56] and is not due to an excessive dietary acid load as subjects were placed on controlled metabolic diets, and urinary sulfate excretion (a marker of dietary acid) was no different. Other possibilities include an increased *endogenous* acid production, intestinal alkali loss, increased absorption of organic acid from the colon, or a combination of the above. However, an increased acid load *per se* does not lower urine pH if the excess H^+ can be adequately buffered. A second defect is required.

Uric acid stone formers have a tendency not to use ammonia to buffer urinary H^+, thus leaving the H^+ free to react with other buffers. From a pure acid–base balance standpoint, this actually suffices. The problem arises, however, when urate gets titrated and becomes insoluble [3]. There is a blunted ammoniagenic or excretory response to an acid load, despite a lower baseline urine pH. Uric acid stone formers exhibit a further drop in their urine pH with an acid load due to insufficient buffer availability, despite a compensatory increase in titratable acid [44]. Calcium oxalate stone formers resemble normals, and subjects with mixed uric acid/calcium stones demonstrated intermediate features.

Some insight into the pathophysiology has been gleaned more recently, in particular as it relates to persons with insulin resistance. Individuals with obesity, metabolic syndrome, or type 2 diabetes have a much higher incidence of uric acid nephrolithiasis at about 30–50 versus 5–8% in the general stone forming population. Conversely, many uric acid stone formers exhibit features of the metabolic syndrome, including impaired glucose tolerance or overt diabetes mellitus, truncal obesity, and hyperlipidemia [28, 57, 58]. Obesity and urine

pH appear to be inversely related [59]. This is due to an increase in net acid secretion without a compensatory increase in renal ammoniagenesis, the cause of which has yet to be elucidated [56]. Work from animal and cell culture models suggests the possibility of renal steatosis and lipotoxicity in the proximal tubule as the cause of the ammoniagenic and excretory defect [60, 61]. The acid–base biochemical abnormalities in uric acid stone formers are summarized in Fig. 3.

A final and third additional factor has to be in place as a low urine pH is so common in subjects with the metabolic syndrome, but most never develop kidney stones. Unduly acidic urine is necessary but not sufficient for uric acid nephrolithiasis. The last unknown factor(s) may reside in an imbalance between inhibitors and promoters and/or epithelial factors. These factors permit adherence, and crystal growth, in order for crystalluria to evolve into a kidney stone. The equivalent lesion of Randall's plaque, a crucial element for calcium oxalate stone formation, has not been described in uric acid stone formers.

Hyperuricosuria and Urine Volume

Hyperuricosuria is commonly defined as a daily urinary urate excretion greater than 800 mg in men and 750 mg in women. Hyperuricosuria *per se* is not the deciding factor for uric acid lithiasis, and conversely, uric acid stones frequently form in patients with normouricosuria. In addition, more deciding than the total amount of uric acid excreted is its concentration in urine. The *solubility* of a substance is defined as the maximum amount that is stable in a solution. *Supersaturation* occurs beyond the solubility concentration, where there is a drive to remove the excess by crystallization, though no new crystals can yet form, until the concentration reaches the *metastable upper limit* (MUL). At and beyond the MUL, crystals will precipitate, enucleate, aggregate, and grow into a urolith.

Urinary concentration of uric acid depends on the amount of uric acid excreted, and the volume of urine produced over that time period. Undissociated uric acid has a solubility of about 100 mg/l, and supersaturation occurs up to about 200 mg/l, where it reaches the MUL. At a urine pH 5.5, 600 mg of uric acid in 1 l of urine would contain 300 mg/l of poorly soluble uric acid. Crystals will form and aggregate to form a stone. At the same pH, an equivalent amount in 3 l of urine would have a concentration of 150 mg/dl. While supersaturated, the urine would not yet reach the MUL, thus no new crystals would precipitate. A diurnal pattern of urine flow has been demonstrated, with the lowest flow and highest osmolarity occurring in the early morning hours (Fig. 4) [34]. The lowest urine volume (highest solute concentrations) also coincides with the lowest urine pH during the early hours of the morning (Fig. 4). Thus, it is the combination of low flow and high osmolarity where hyperuricosuria leads to precipitation of crystals. While hyperuricosuria is an established risk factor for uric acid stones, it will more commonly result in calcium oxalate nephrolithiasis (hyperuricosuric calcium urolithiasis) [39], though a recent analysis has questioned this association [62]. This is described in detail elsewhere.

Monogenic enzymatic disorders, such as the Lesch-Nyhan syndrome and some types of glycogen storage diseases, are rare causes of severe hyperuricemia and hyperuricosuria and will not be discussed in this review.

Etiology of Uric Acid Nephrolithiasis

Idiopathic Uric Acid Nephrolithiasis

This largest group of patients has no identifiable secondary cause for the development of uric acid stones. Clinical gout is not present, but it resembles primary gout in many aspects, for which reason the term “gouty diathesis” (latent gout) has historically been used [43]. The similarities to gout include a persistently low urine pH, a reduced fractional excretion of uric acid, and varying degrees of hyperuricemia. However, individual values overlap considerably between this group and controls.

Persons with the metabolic syndrome share many characteristics with idiopathic uric acid stone formers, but they do not necessarily form uric acid stones. Nevertheless, in one study of unselected uric acid stones formers, more than 50% were either overtly diabetic or had impaired glucose tolerance [44]. In clinical practice, it is rare to encounter a uric acid stone former with absolutely no features of the metabolic syndrome.

Primary Gout

Men have higher uric acid levels than women, and hyperuricemia is commonly defined as a serum level greater than 7 mg/dl in men and 6 mg/dl in women. Gout is about five times more common in men, however, while hyperuricemia is in fact the most important risk factor for the development of gout, most persons with hyperuricemia do not develop gout. Only about 10–20% of patients with gout develop kidney stones. Several factors play a role, such as diet (high-purine diet, fructose sweeteners, alcohol consumption), and genetic aspects, as it has a familial incidence of up to 30%. As in gouty diathesis (idiopathic uric acid nephrolithiasis), it is associated with a low urine pH, hyperuricemia, and normouricosuria or hypouricosuria due to a low fractional excretion of uric acid, though in some individuals, hyperuricosuria is present [18]. The universal and obligatory finding is always the presence of an acidic urine [44]. Considering the large number of overlapping features, it may not be justifiable to distinguish gout from idiopathic uric acid nephrolithiasis based solely on the presence or absence of gouty arthritis.

Rare Mendelian Disorders

Monogenetic disorders associated with hyperuricemia and a low fractional excretion of uric acid, such as medullary cystic kidney disease and familial juvenile hyperuricemic nephropathy due to a mutation in the uromodulin gene (Tamm-Horsfall protein), have been well described [63, 64] and will not be discussed in this review.

Gastrointestinal Disorders

Alkaline pancreatic and biliary secretions neutralize acidic gastric secretions, and HCO_3^- absorption in the small intestine keeps bicarbonate loss in normal stool to a minimum. Gastrointestinal losses of alkali (bicarbonate) or “potential alkali” (organic base) are commonly associated with systemic metabolic acidosis, a low urine pH, hypocitraturia, and low urine volumes, which predispose to both uric acid and calcium oxalate stones [65]. Examples include intestinal fistulas, ostomies, or certain types of diarrhea. Osmotic diarrhea due to water-soluble solutes such as magnesium, lactulose, and polyethylene glycol produce

little loss of bicarbonate, and patients do not develop a metabolic acidosis. However, chronic diarrhea due to active secretion of electrolytes (secretory diarrhea) can produce large losses of various electrolytes, as well as bicarbonate. Osmotic diarrhea can be seen with certain laxatives (senna, bisacodyl), bile acids or fatty acids (short gut syndrome), infections, or inflammatory bowel disease, and is strongly associated with uric acid stones The loss of alkali can be up to several 100 mmoles per day under extreme circumstances.

Neoplastic Disorders

Myeloproliferative disorders and solid tumors with a large cell mass often exhibit overproduction of uric acid due to high cell turnover with release of nucleic acids, producing both hyperuricemia and hyperuricosuria. This may lead to acute tumor lysis syndrome with initiation of chemotherapy. Complications include acute urate nephropathy due to precipitation of uric acid and calcium phosphate crystals, and uric acid stones [66]. Other examples of high cell turnover are hemolytic anemias, in particular sickle cell disease, where hyperuricosuria has been reported, though the incidence of uric acid stone formation is uncertain [67].

Diet

Low-carbohydrate high-protein diets are popular for weight reduction. The protein (purine) load increases uricosuria and decreases urinary citrate and pH [68]. It is commonly believed that overindulgence with purine-rich foods leads to uric acid stones. However, since ammoniagenesis is intact, adequate buffer production mitigates the fall in urine pH. Thus, much more common are hyperuricosuria-associated calcium oxalate stones (hyperuricosuric calcium urolithiasis) [69].

Persons with primary gout as well as “latent gout” (gouty diathesis) frequently exhibit features of the metabolic syndrome, and dietary indiscretion may be part of their lifestyle. Thus, the combination of the defects of the metabolic syndrome and a high-purine diet constitutes a particularly high risk for uric acid lithiasis [42].

Evaluation

The evaluation of uric acid nephrolithiasis starts with a complete history and physical exam with special attention to secondary factors that may contribute to uric acid lithiasis, such as the presence of diabetes mellitus, the metabolic syndrome, or gouty arthritis. Patients may have a history of cancer, chronic diarrhea and malabsorption (including short gut syndrome), inflammatory bowel disease, or intestinal surgery, in particular small bowel ostomy. A family history may be positive, especially among male first degree relatives. The history should also include a careful review of the patient’s diet, in particular the currently popular high-protein, low-carbohydrate diets, fluid intake, fluid losses (exercise), alcoholic beverages, and all medications, including over-the-counter preparations.

A history of possible stone passage is helpful in making the diagnosis. The pain due to uric acid stone passage is indistinguishable from other stones. The patient may experience nausea, emesis, and sometimes gross hematuria (brownish, tea-colored or “Coke”-colored urine).

Physical findings are not specific for uric acid versus other stones other than the prevalent presence of obesity and other features of the metabolic syndrome or diabetes. In severe gout sufferers, tophi may be present.

Initial blood chemistries should include electrolytes, glucose, and uric acid. A lipid profile may indicate hypertriglyceridemia and low HDL as part of the metabolic syndrome. Even a simple urine dipstick will show low a urine pH, frequently 5.5 or lower. Spot urine with prolonged exposure to room air may lose CO_2 and alkalinize. Microhematuria may or may not be present. Acidic urine frequently contains uric acid, calcium oxalate, or amorphous urate crystals. Sodium urate crystals are less common. Uric acid diamond, rhombic prism, or a cluster of crystals (“rosette”) [70]. Uric acid crystals stain with urine pigment and retain a yellow to brown color. However, the mere presence of uric acid crystalluria does not imply that the patient has uric acid stone disease. Urate salts of sodium or potassium assume a non-crystalline, amorphous form of yellowish or yellow-reddish coloration. Sodium urate may form needles or slender prisms in clusters.

Some patients may present with a passed stone that can be sent for analysis by infrared or X-ray diffraction. Unlike the sharp and jagged calcium oxalate calculi, uric acid stones tend to be smoother, though not invariably so. Uric acid stones can range from a small rounded pebble to a fully branched staghorn.

Even if a patient is able to provide a stone for analysis of its composition, a 24 h urine collection for stone risk analysis is essential to provide insight into the pathophysiology of stone formation in a particular patient. The collection quantifies urine volume, pH, creatinine, calcium, oxalate, citrate, uric acid, sulfate, chloride, and ammonium. It calculates the relative supersaturation (RS) as the ratio of the activity product (the concentration of undissociated uric acid) to the corresponding mean activity product (of undissociated uric acid) arbitrarily defined from normal subjects. Urine pH of 5.5 or lower is quite typical for uric acid nephrolithiasis. When in balance, net acid excretion, ammonium plus titratable acid minus base equivalent (citrate and others), is a reflection of net acid production. Sulfate excretion is a marker of dietary acid intake from proteins. A high-protein diet also results in a high urine urea and uric acid excretion. Urinary potassium is a surrogate marker for dietary alkali intake. In metabolic studies, the ratio of ammonium-to-net acid excretion in urine tends to be lower in uric acid stone formers. Whether this parameter can predict uric acid stones has yet to be tested in a clinical setting.

For evaluation of a patient with an acute colic, non-contrast enhanced computer tomography (CT) of the kidneys (“renal stone protocol”) is the method of choice, as it has a high specificity and sensitivity even for small stones, or stones located in the ureters. It will also readily detect radiolucent stones such as pure uric acid. The density reading in Hounsfield units (HU) is high for all stones, which distinguish them from other fillings defects such as a blood clot, a tumor, or a sloughed renal papilla. A “renal stone protocol” CT of the kidneys and ureters is also essential to determine whether a patient is a suitable candidate for lithotripsy based on size and location of the stone, or whether ureteroscopic stone removal is more appropriate. Intravenous pyelography (IVP) is now rarely used.

For outpatient evaluation of a patient who is currently free of symptoms, renal ultrasonography is typically the initial study, because of its wide availability, low cost, and absence of exposure to radiation. For the same reasons, it is also the preferred imaging method for follow-up monitoring of established uroliths. All stones, including uric acid, have a classic finding of a densely echogenic focus within the renal pelvis, with characteristic post-acoustic shadowing. A plain radiograph of the abdomen for kidney-ureters-bladder (KUB) is rarely used for initial screening. Pure uric acid stones are radiolucent on plain radiographs, but radiopaque if they are mixed uric acid/calcium oxalate. The differential diagnosis of radiolucent stones includes xanthine stones in patients with high uric acid production plus concomitant therapy with a xanthine oxidase inhibitor, such as allopurinol or febuxostat. In hereditary xanthinuria, there is little production of uric acid, and patients present with hypouricemia. Unlike uric acid stones, the rare xanthine and 2,8-dihydroxyadenine (2,8-DHA) stones do not dissolve in an alkaline milieu, and thus, do not respond to therapy with alkali [71].

Management

The management of acute renal colic in uric acid stones is not different from other stones using medical expulsion therapy [72] and will not be further discussed here.

General Stone Clinic advice holds true for uric acid stone formers as well, in particular, maintaining a urine volume of at least 2 liters per day to reduce supersaturation of the lithogenic constituents of urine. A reduced daily protein intake to 0.8 g per kg body weight (or less) increases urine pH as it reduces the exogenous acid load imposed on the body. It also improves uricosuria. However, this mode of therapy has never been tested in uric acid stone formers. In addition, hyperuricosuria is not typically a feature of uric acid nephrolithiasis, as outlined earlier. Nevertheless, hyperuricosuria does contribute to the amount of undissociated uric acid in the urine, and limiting the ingestion of high-purine food items (red meat, poultry, some fish) is likely beneficial.

Several studies have shown that xanthine oxidase (XO) inhibition is effective in reducing urinary uric acid but these trials were designed for hyperuricosuric calcium oxalate stone formers [72, 73]. Febuxostat appears to be as effective as allopurinol in its ability to lower plasma uric acid, but the hypouricosuric effect remains to be proven [74]. For uric acid stone formers, mere hyperuricosuria (greater than 800 mg in men and 750 mg in women) should rarely be treated with XO inhibitors, unless clinical gout is present, or hyperuricosuria is severe. They are always indicated in patients with hyperuricosuria due to inborn errors of metabolism, myeloproliferative disorders, some hemolytic anemias (in particular sickle cell anemia), and as a preventative measure for tumor lysis syndrome. For the latter, recombinant uricase (rasburicase) is typically preferred as it metabolizes uric acid to the much more soluble allantoin and avoids the risk of xanthine stone formation.

Idiopathic uric acid nephrolithiasis and gout cover the vast majority of patients with uric acid stones. In these patients, overly acidic urine (a urine pH below 5.5) is the principal abnormality, so therapy is targeted at raising the urine pH. Alkali therapy to maintain a 24-h urine pH between 6.0 and 6.5 is effective at reducing stone recurrence and new stone

formation from 1.20 to 0.01 stones per year [45, 75]. Alkali therapy can even dissolve existing pure uric acid stones, but not calcium containing stones [76]. To raise the urine pH, the standard protocol uses potassium citrate at an initial dose of 30–40 mEq per day, and a typical final dose between 30 and 80 mEq per day. This should be administered in two or three daily doses to maintain an alkaline urine pH throughout the day. Sometimes, an evening dose of K citrate is necessary to prevent nocturnal aciduria [52]. As outlined earlier, the lowest urine volume, and thus the highest solute concentrations, coincides with the lowest urine pH during the early morning hours. Self-administered pH measurements by urinary dip-sticks help guide therapy as they allow for adjustment of medication dosage as needed throughout the day [52, 77].

For pH measurements, 24-h urine collections may not adequately reflect the diurnal variations in urine pH, where short periods of extreme acidity can lead to stone formation or growth of existing stones [34, 52]. Treatment with base should achieve a goal urine pH above 6.1, but less than 7.0 to avoid the complication of calcium phosphate stone formation.

While potassium citrate is the standard of therapy, alternatives include potassium bicarbonate, sodium citrate, or even sodium bicarbonate. Sodium citrate and bicarbonate have fewer gastrointestinal side effects and are often better tolerated than the potassium salts. In addition, for patients with impaired renal function and a tendency to hyperkalemia, any additional potassium may not be feasible. However, an important shortcoming of all sodium alkali salts is the fact that they promote an increase in urinary calcium excretion, and thus a predisposition to calcium stone formation [78]. In addition, sodium urate is less soluble than potassium urate. Urinary alkalinization with sodium alkali salts in the presence of high urine sodium is not favored. In addition, sodium bicarbonate tablets provide only 3.8 or 7.6 mEq of bicarbonate per tablet, and thus, the pill burden is significant. Baking powder is an alternative, in particular if cost concerns are an issue, but it provides 70 mEq of bicarbonate per flat teaspoon and has to be taken very judiciously and in divided doses throughout the day.

Carbonic anhydrase inhibitors (acetazolamide, topiramate) are not recommended as they induce systemic metabolic acidosis and hypocitraturia and increase urinary saturation of calcium salts [45]. In combination with the higher urine pH, calcium phosphate stones may form.

A non-pharmacologic way of alkalinizing urine includes orange juice due to its high content of potassium citrate. Lemons contain mainly citric acid, and thus, lemonade is much less effective in raising urine pH [79]. Fruit juices deliver a significant caloric load. This is particularly detrimental for acid stone formers, as it is rare to find no features of the metabolic syndrome in these patients. Any further weight gain will likely exacerbate the metabolic derangements and tendency to form stones. Emphasis should be placed on weight reduction and improvement of insulin resistance. In fact, improving the systemic metabolic disorder may the single most important measure an individual can undertake for the prevention of uric acid nephrolithiasis.

In conclusion, the inability to metabolize uric acid due to the mutational loss of a functioning uricase in humans and some higher primates millions of years ago results in high serum levels of uric acid, and clinical disease such as gout and uric acid nephrolithiasis. Uric acid nephrolithiasis is essentially the renal manifestation of a systemic metabolic disorder. The primary driver for uric acid stones is a low urine pH, leading to precipitation of insoluble uric acid. Less deciding factors are hyperuricosuria and low urine volume. Stone formers exhibit a lower baseline urine pH due to increased acid production and the relative inability to respond to an acid load with a compensatory increase in urinary buffers. Individuals with the metabolic syndrome comprise the largest group of uric acid stone formers, and the vast majority has either primary gout or idiopathic uric acid nephrolithiasis; less common are gastrointestinal or neoplastic disorders. Management comprises a liberal fluid intake to increase urine volume, and alkalinizing measures to raise to urine pH to 6–6.5, preferably with potassium citrate, though sodium citrate and bicarbonate are alternatives. Finally, dietary modification is recommended, though there is insufficient data in regards to its effectiveness for the prevention of uric acid lithiasis.

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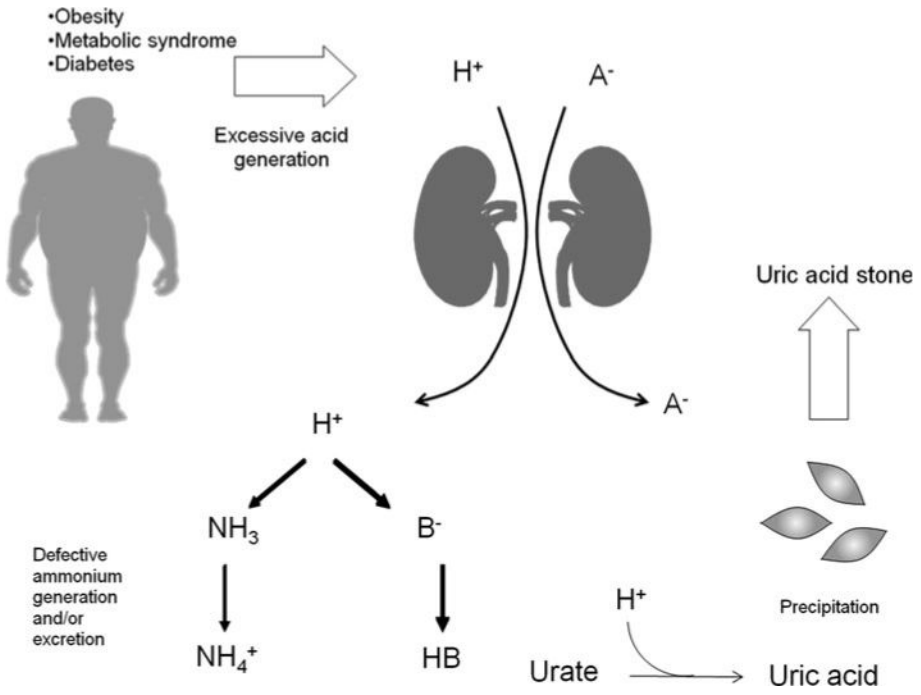

Fig. 1.

Events leading to titration of urate to uric acid in urine. Acid generation is increased in obesity, metabolic syndrome, and type 2 diabetes mellitus. The excess H^+ is excreted in the urine but the increase in net acid excretion is not entirely mediated by increased ammonia synthesis and ammonium excretion. This leaves excess H^+ to titrate other buffers, which fulfills acid–base balance. However, one such buffer is urate, which can precipitate when protonated to the highly insoluble uric acid. Additional but yet unidentified factor(s) enable uric acid crystals to become uric acid stones

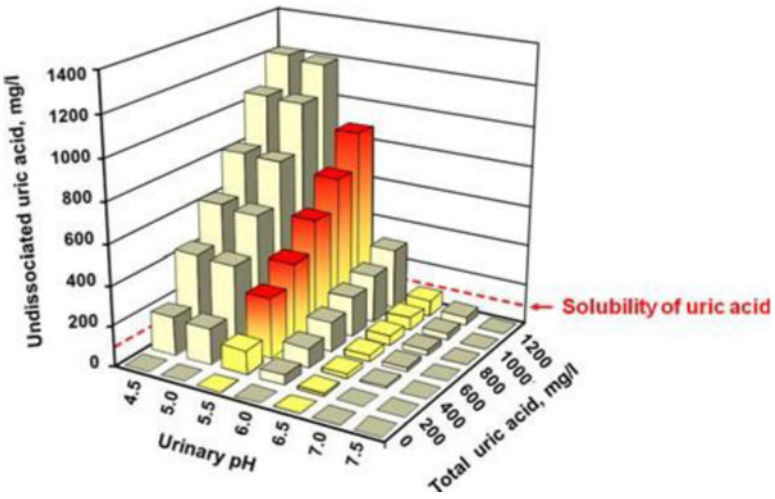

Fig. 2.

The relative effects of urine pH and total uric acid on undissociated uric acid (modified from Maalouf et al. with permission). The quantitative relationship of urate, uric acid, and pH are determined by the pKa of 5.3. The *dashed line* denotes the solubility of uric acid. At a urine pH of 6.5, even a high level of uricosuria does not significantly elevate undissociated uric acid. At a urine pH of 5.5, even a modest concentration of uric acid within the clinical normal range will lead to an undissociated uric acid level that far exceeds its solubility. With permission from Maalouf N et al. (*Credit to*: Maalouf N, Gaska MA, Abate N, Sakhaae K, Moe OW. New insights in the pathogenesis of uric acid nephrolithiasis. Curr Opin Nephrol Hypertens 13:181–189, 2004)

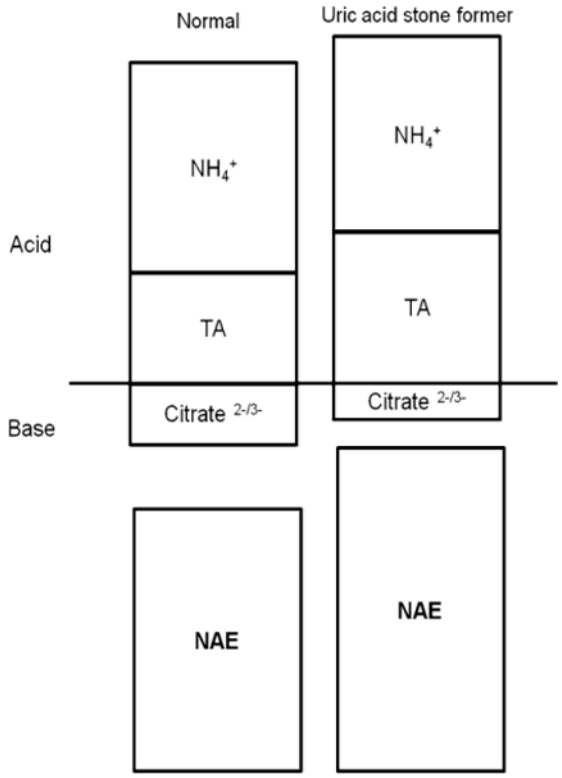

Fig. 3.

Acid base parameters in normal individuals and uric acid stone formers. *TA* Titratable acidity, *NAE* Net acid excretion, estimated as $NH4^+$ + TA—base (citrate and others)

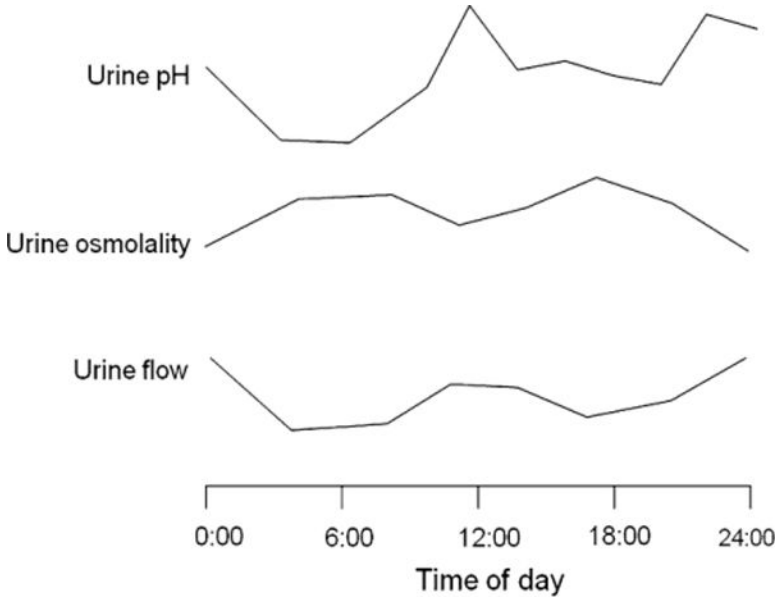

Fig. 4.

Diurnal variation of urine pH and volume. In the early hours of the morning, both urine pH and urine volume are lowest, rendering this a particular vulnerable period for uric acid precipitation