Curr Rheumatol Rep (2010) 12:125–129
DOI 10.1007/s11926-010-0089-y

Update on the Pathophysiology and Management of Uric Acid Renal Stones

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Published online: 3 March 2010

Abstract Idiopathic uric acid nephrolithiasis appears to be increasing in prevalence. While it has long been known that low urine pH is associated with uric acid stones, only recently has the pathophysiological basis for this disease emerged. Excessively acidic urine is the decisive risk for uric acid lithogenesis, and patients with diabetes and the metabolic syndrome often hold the company of low urine pH. While association does not imply causation, interesting insights have been made regarding insulin's influence on acid-base physiology. We review recent evidence from both the molecular and clinical realms to underline the importance of [H+] in the development and treatment of uric acid nephrolithiasis.

Keywords Allopurinol · Febuxostat · Gout · Nephrolithiasis · Urine pH · Urolithiasis

Introduction

Hyperuricosuria is not the cardinal risk for the development of uric acid stones. Instead, the overriding pathophysiological process is the unduly acidic urine. [1] Epidemiological data from converging sources have featured obesity, type II diabetes mellitus, and the metabolic syndrome as strong associates with low urine pH. [2–5] Interestingly, with the obesity epidemic in the United States, the incidence of nephrolithiasis has grown in parallel (Flegal et al 2002; Asplin 2009).[6, 7•] Originally the association between adiposity and urine lithogenicity was thought secondary to an increase in calcium oxalate stones via relationships between body mass index (BMI), hyperoxalauria [8], hyperuricosuria [9], and hypercalciuria. [10]. It was subsequently found that increased calcium excretion in the obese co-varied with intake of animal protein and sodium; no relationship was found between BMI and urinary supersaturation of calcium oxalate. These results suggested that the augmented incidence of nephrolithiasis in the obese is secondary to uric acid stones [2].

With the proportion of obese Americans increasing and the association of obesity and the low urine pH, uric acid nephrolithiasis is of paramount interest to the rheumatologist and internist alike. We will review the clinical presentation and basic diagnostic approach to nephrolithiasis. Emphasis will be placed upon uric acid stones. The basic biochemistry, physiology and etiology of uric acid nephrolithiasis will be delineated with special attention paid to novel pathophysiological mechanisms and essential therapeutic strategies.

Presentation and Diagnosis

Most patients who present with an acute kidney stone have downward-radiating flank pain progressing anteriorly into the abdomen, pelvis and genitals as the stones advances down the ureter. [11] The pain is usually abrupt, colicky

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and can be grossly localized to a particular portion of the urinary tract based on symptoms [12]. The clinician should focus on a differential diagnosis including: pyelonephritis, gynecological or intra-abdominal catastrophes, prostatitis, and expanding or ruptured aortic aneurysm. The focused history should thus include specific urinary symptoms, fevers, change in bowel habits, recent instrumentation and previous history of renal colic and stones. Notably, men with a history of smoking and new onset flank or back pain after the age of 60 should have an aortic evaluation. [13] Medications should be reviewed for uricosuric agents such as probenecid, high-dose salicylates, and losartan [1, 14].

Computed tomography (CT) is the gold standard for the diagnosis of renal colic; plain films will not detect radiolucent stones without calcium, like pure uric acid nephrolithiasis. [11] The laboratory evaluation of acute renal colic should include basic laboratory studies of the serum as well as calcium, phosphorus, and uric acid. Urinalysis should also be obtained with emphasis on pH as discussed below. Preventive therapy in patients with recurrent stone burden, by contrast, necessitates determination of stone composition, and urine supersaturation in 24-hour urine collections.

Uric Acid Biology

Roughly 10% of stones in the United States are uric acid [15], but uric acid may cause salting out of calcium oxalate salts and therefore contribute to the incidence of the more prevalent stone population. There is considerable variability in the proportion of uric acid stones within different geographies and this likely reflects differences in the pathophysiology of uric acid stones detailed below [16, 17].

Uric acid is diprotonated with a pKa1 of 5.3 and pKa2 of >10 at 37 degrees Centigrade. It is the behavior of the former proton that is responsible for uric acid urolithiasis. At a pH above its pKa1, uric acid exists as urate, its deprotonated, charged and therefore water-soluble form. As the ambient pH decreases and approaches 5.3, the equilibrium shifts to the protonated, insoluble form and uric acid crystals precipitate.

Xanthine oxidase (XO) catalyzes the conversion of xanthine to uric acid. Xanthine is a byproduct of purine synthesis. It follows that in states of purine gluttony or in states of rapid cell turnover, this pathway is mobilized. The degree to which the kidneys and intestines eliminate the uric acid load determines the likelihood of hyperuricemia. [18] Uric acid elimination by the kidneys handles nearly 70% of the total uric acid load and follows a complex reabsorption, secretion and post-secretory reabsorption process in the proximal convoluted tubule (PCT) rendering the normal fractional excretion of uric acid about 10%. [18, 19] Uric acid transporters are localized to both the apical and basolateral membranes of PCT epithelial cells and are coupled to sodium and organic ion transport. The inhibition of the apical membrane URAT1 transporter by probenecid, NSAIDs, salicylates and losartan can worsen hyperuricosuria [19].

Pathophysiology of Uric Acid Nephrolithiasis

There are three urinary contributors to uric acid nephrolithiasis—hyperuricosuria, low urine volume and aciduria. The latter is considered necessary, as the precipitation of uric acid is unlikely at a higher urine pH.Elevated urine uric acid is generally defined as more than 600–700 mg in 24 h. [20] While elevated uric acid contributes to uric acid stone formation, supernormal levels can be tolerated within typical values of urinary pH. [1] Indeed, hyperuricosuria as the sole cause of uric acid nephrolithiasis is considered relatively rare [18].

Elevation of urinary uric acid concentration may arise from both congenital and acquired causes. Congenital conditions are atypical and unlikely to be encountered in the clinic setting. Irregularities in purine metabolism (e.g. Lesch-Nyhan, Kelley-Seegmiller, 5′-phosphoribosyl-1′-pyrophosphate synthetase over-activity), select glycogen storage diseases, and uric acid transporter mutations elevate urinary uric acid levels. [18] Acquired causes of hyperuricosuria include dietary indiscretions, malignancy and chemotherapy and uricosuric medicines. For example, participants who ingested purine-rich as compared to purine-free diets demonstrated a 50% or greater increase in urinary uric acid excretion with simultaneous elevations in serum uric acid. [21, 22] Primary gout patients have been found not to exhibit elevated urinary uric acid excretion. [23, 24] By contrast, primary gout patients have been found to have acidic urine, the importance of which is discussed below [23, 25].

Low urine volume also predisposes to uric acid stone formation. By increasing the relative saturation of stone-forming constituents, a urine volume less than 2 L/day promotes the development of all kidney stones. This observation may partly explain the increased incidence of stone formation in professions with increased insensible water loss (e.g. lifeguards) and in populations closer to the equator. [26] Chronic diarrhea, in patients with ileostomies or short bowel syndrome, or affected by inflammatory bowel disease, who lose bicarbonate-rich bowel effluent, have low urine volume and pH, both of which encourage uric acid precipitation [7].

The overriding risk for uric acid nephrolithiasis is the unduly acidic urine. Low urine pH leads to stone

precipitation with relatively modest amounts of uric acid excretion while urine pH above 6.0 requires large amounts of urinary uric acid for lithogenesis. the correlation between acidic urine and the metabolic syndrome has only recently been elucidated. In two large cohorts of uric acid stone formers there was a strong negative correlation between BMI and urine pH. [5] Additionally, each component of the metabolic syndrome appears to confer a risk for more acidic urine. [3••] The putative pathophysiology is that of impaired ammoniagenesis. Classically, ammonia can be considered a buffer of urinary protons. Low ammonium production, therefore, leaves free protons to be buffered by titratable acids (e.g. phosphates and sulfates) thereby lowering urine pH. Reabsorption of filtered citrate, a form of potential base, is stimulated in the proximal tubule in states of acidosis or acid loads and hypocitraturia results. Indeed hypocitraturia is commonly found in these patients (Taylor & Curhan 2006; Abate et al. 2004) and it is also a raises the risk of calcium stone formation as citrate is an important inhibitor of calcium salt crystal formation [2, 27].

The link between metabolic syndrome and impaired ammoniagenesis is thought mediated by insulin resistance. [4, 24, 28] Multiple theories have been advanced. Firstly, insulin was thought to promote the deamination of glutamine to glutamate and then to alpha-ketoglutarate. [29, 30] Secondly, the PCT cells use glutamine as an energy source under normal conditions. Elevated free fatty acids, as seen with diabetes, inhibit this means of metabolism and shift equilibrium away from ammonium production. [31] Finally, insulin was shown in animal models to stimulate the activity of the Na+/H + antiport in the PCT. [32, 33] The proton excreted into the tubular lumen traps ammonia as ammonium, and consequently promotes acid excretion. Clinically, normal controls increased urinary ammonium excretion and raised urinary pH under a hyperinsulinemic, euglycemic-clamp protocol, while uric acid stone formers had a blunted response. [27] Of further note in this study, non-stone forming diabetics, like non-diabetic stone formers, had evidence of insulin resistance, but a normal increase in their urinary ammonium in response to insulin infusion. What differed between these groups was the presence of hyperuricemia in the stone formers. The signal transduction of insulin is nitric oxide dependent, and uric acid has been shown to disrupt this process. [34] This finding places uric acid itself as a potential culprit for insulin resistance. Interestingly, this uric-acid mediated toxicity has been localized to the PCT [35].

While impaired insulin induced proton extrusion may be the basis of this PCT defect, so too may be lipotoxicity. This phenomenon, simply, is the accumulation of fat in non-adipocyte tissues and has been postulated to disrupt normal cellular biochemistry. Indeed, this has been observed in rats as PCT fat accumulation was shown to impair Na+/H + exchange at the luminal surface. [36••, 37] This, in turn, would prevent both the ammonium ‘trap’ and ammonia excretion at the PCT.

Impaired ammoniagenesis is not the only pathogenic feature of patients with abnormally low urine pH. Increased net acid excretion (NAE) and titratable acidity has been observed in uric acid stone formers as well , even on fixed diets. [20, 27, 28] The biochemical origin of these findings is unclear but may be related to endogenous organic acids [38], or impaired post-prandial alkaline tide [39, 40].

Therapy

The treatment of uric acid nephrolithiasis may be approached in terms of lifestyle modification, pharmacologic reduction in uric acid excretion, and urinary alkalinization. [18] The latter is most important and clinically appears to be the most effective. If alkalinization is achieved, the importance of the other manipulations is less certain.Alkalinization can be achieved with potassium citrate in varying doses, from 20 to 40 mEq once or twice a day. Potassium citrate is preferable to sodium citrate, as the sodium excretion may be associated with increased calciuria, though in non-calcium stone formers this problem may not be important. Some patients with heart disease and hypertension may not tolerate the sodium loads, but hypertension, hypervolemia and pulmonary congestion are observed less often with bicarbonate salts than with sodium chloride indiscretions. Patients with decreased glomerular filtration rates or taking angiotensin converting enzyme inhibitors and angiotensin receptor blockers may not tolerate the potassium load. The comparative efficacy of potassium and sodium citrate in achieving alkalinization is probably similar. While potassium and sodium bicarbonate may also be used, the bicarbonate is titrated by stomach acid into carbon dioxide gas and leads to gastrointestinal complaints more so than citrate salts.

When initiating urinary alkalinization therapy, 24 h urine pH can be monitored and maintained between 6.1 and 7.0 as excessively low urinary [H+] can lead to hypocitraturia and calcium phosphate precipitation (Coe et al. 2005). However, alkalinization need not be achieved for the entire 24 h period; achieving a urine pH of 6.5 once a day or even every other day may be sufficient to prevent stones. [41, 42] Our practice for attempting to dissolve existing stones is to achieve round-the-clock alkalinization and use nightly citrate administration for prevention. By measuring urine pH at home once a day at varying times for a few weeks patients can determine whether urine pH has been sufficiently increased. Inexpensive test paper can be purchased for easy measurement at home (for example, Item #067,

http://microessentiallab.com, Micro Essential Laboratory, Brooklyn, NY).

Carbonic anhydrase inhibitors such as acetazolamide may also be used to raise urinary pH. However, problems with overly alkaline urine and a risk for calcium phosphate stones then occur. In addition, the induction of systemic metabolic acidosis is undesirable. Acetazolamide is generally reserved for patients who have difficulties with potassium and sodium citrate or bicarbonate.

Lastly, various citrus juices and beverages have urinary alkalinizing effects by virtue of their citrate content and although their effects on stone formation have not been tested, they might be useful adjuncts to achieve an alkaline urine. [43] Orange and grapefruit juice and sports drinks have been shown to exert both citraturic and alkalinizing effects. [44–46] Lemon juice, with a lower pH, delivers less of a net alkaline load [44].

Fluid intake should be increased to maintain a urinary volume of approximately 2 L/d and the diet should be modified to decrease consumption of animal proteins. The Recommended Dietary Allowances (RDA) for protein intake is 0.8 g/kg/d.

Reduction of uric acid levels can be achieved through diet,or through medication. Both allopurinol and febuxostat are XO inhibitors and significantly decrease hyperuricemia and hyperuricosuria. [47] As specified above, reduction of urinary uric acid levels would only be beneficial in the treatment of uric acid stone disease once abnormally low urine pH is corrected and if urinary uric acid levels are high. We reserve XO inhibitors for patients who have difficulty achieving an alkaline urine, such as patients with bowel disease, or in patients who continue to have uric acid stones despite successful alkalinization. The efficacy of febuxostat has only been examined in primary gout, and has not been tested in uric acid nephrolithiasis. Nevertheless its potential importance lies in its hepatic metabolism as it can be given to patients with chronic kidney disease. It may therefore carry a lower side-effect profile including the risk of Stevens-Johnson syndrome in such patients

Conclusion

With the rising incidence of obesity, type 2 diabetes and the metabolic syndrome, clinicians will continue to encounter newer renal manifestations of insulin resistance: low urinary pH and uric acid nephrolithiasis. Uric acid stones may be recognized as a marker for insulin resistance and a presenting symptom of diabetes and metabolic syndrome. While the etiology of the unduly acidic urine remains unclear it likely lies within the realm of insulin's effect on acid-base physiology. Uric acid stone formers have biochemical and metabolic aberrancies consistent with those seen with the metabolic syndrome. However, the latter is neither necessary nor sufficient for uric acid lithogenesis. Questions remain regarding the inciting factors for stone formation. Dothey include a direct effect of uric acid on the insulin receptor and does a lack of unknown urinary inhibitors of uric acid crystal precipitation contribute? Does treatment of insulin resistance lower stone incidence? Until these questions are answered, management of the known instigators—low urine volume, hyperuricosuria and, most importantly, low urinary pH can reduce the burden of uric acid stones.

Disclosures Dr. Goldfarb: medical advisory boards for Takeda and Sanofi-Aventis; consultant for Watson; research funding from NIDDK and Office of Rare Disease Research.

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