Clinical study of ammonium acid urate urolithiasis

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KEYWORDS
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Abstract Ammonium acid urate (AAU) urolithiasis is a rare condition; however, it is endemic in some countries, with an especially high incidence in Asia. This study was conducted to investigate the special presentation of patients with AAU urolithiasis in Taiwan. Reports of 3457 stones were retrospectively reviewed from January 2005 to January 2010 and 25 patients with urinary stones (0.7%) containing AAU crystals were identified. The clinical and biochemical presentation of all stones were compared to evaluate the specific comorbidities of AAU stones. AAU stones were observed in 11 males (44%) and 14 females (56%) with a mean age of 60.60 ± 16.81 years and mean body mass index of 25.55 ± 3.73 kg/m². AAU stones were frequently observed in the bladder (44%) and they were significantly larger (mean size 1.90 cm) than the non-AAU stones (mean size 1.22 cm). Other significant comorbidities of AAU stones included chronic kidney disease (CKD) (60%), urinary tract infections (UTIs) (52%), irritable bowel syndrome (IBS) (36%), and gout (28%). In addition, there were also three patients with coexisting urothelial carcinoma (12%) in the AAU-stone group. Patients with AAU urolithiasis were predominantly female, older in age, had increased bladder presentation, larger stones and a high percentage of coexisting CKD, UTIs, IBS, gout, and even urothelial carcinoma. Therefore, it is important for clinicians to evaluate and protect renal function in patients with AAU urolithiasis.

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Introduction

Urolithiasis is a disorder that is increasing in prevalence in the tropics as well as in most Western countries [1]. The lifetime prevalence of symptomatic urolithiasis is 5% to 10% worldwide, with a male predominance; however, the incidence of urolithiasis is increasing. Unlike common calcium-containing stones, ammonium acid urate (AAU) urolithiasis is quite rare in patients with urinary stones (< 1%) [1]; however, AAU urolithiasis is still observed in developing countries, especially in Asia [2]. Urolithiasis generally arises from disturbances of the physiochemical balance and the hydrodynamic system in the urinary tract. Some studies have reported special risk factors for AAU urolithiasis, including irritative bowel syndrome (IBS), laxative abuse, obesity, urinary diversion, pregnancy, chemotherapy, and recurrent urinary tract infections (UTIs) [3–5]; however, idiopathic AAU crystals may also develop in the absence of these risk factors. The actual etiology and pathophysiology of stones containing AAU crystals are still not completely understood. Hence, the present study aimed to investigate the clinical and biochemical presentation of AAU urolithiasis in Taiwan.

Methods

This study was approved by our hospital’s institutional review board. From January 2005 to January 2010, 3457 patients were diagnosed with urolithiasis and underwent stone analysis at Kaohsiung Medical University Hospital and Kaohsiung Municipal Hsiao-Kang Hospital. They were stratified into two groups according to whether or not their stones contained AAU crystals. The hospital charts of all patients were reviewed for socio-demographic characteristics, detailed physical examination results, body mass index (BMI), and medical history. Biochemical analysis of blood samples, including creatinine, calcium, uric acid, and urine pH (the first morning urine sample), was also collected. The glomerular filtration rate (GFR) was calculated with the Cockcroft-Gault equation. Stone presentation was evaluated in terms of their size, site, and number, using a kidney–ureter–bladder film or ultrasonography to obtain a definitive diagnosis. The composition of all stones was analyzed by infrared spectrophotometry (Spectrum RX I Fourier Transform-Infrared System, Perkin Elmer, USA). Potential comorbid risks that may be associated with AAU stones were performed using chart review and telephone interviews. Obesity was defined as a BMI of >27 kg/m². Gout was defined as a history of hyperuricemia and clinical arthropathy. Laxative abuse was defined as taking laxatives without a prescription [6]. IBS was defined on the basis of the Rome III criteria [7]. Patients with renal failure, renal tubular acidosis, hyperparathyroidism, or osteoporosis and those using medications such as diuretics, vitamin D or calcium supplements were excluded from the study. The demographic and clinicopathologic characteristics of the patients in the two groups were compared using Pearson’s Chi-square test or Student t test. Statistical analyses were performed using JMP v8.0 statistical software. For all statistical analyses, \( p < 0.05 \) was considered statistically significant.

Results

As AAU stones are difficult to differentiate from other stones through gross examination, we analyzed stone composition with infrared spectrophotometry (Fig. 1). Among the 3457 patients with urolithiasis, 28 calculi from 25 patients (0.7%) contained AAU crystals. These patients consisted of 11 males (44%) and 14 females (56%) with a mean age of 60.60 ± 16.81 years and a mean BMI of 25.95 ± 3.73 kg/m². The mean serum creatinine and GFR levels were 1.24 ± 0.45 mg/dL and 59.57 ± 26.56 ml/min, respectively. The clinical characteristics and laboratory data of the patients with stones, categorized by the presence or absence of an AAU crystal, are shown in Table 1. The patients with AAU stones were significantly more likely to be female (\( p = 0.002 \)), of older age (\( p = 0.008 \)), and have a lower mean GFR (\( p = 0.002 \)) than those with non-AAU stones. However, the BMI, family history of urolithiasis, urine pH, serum uric acid, and serum calcium levels of the two groups were similar. Although 429 cases in the non-AAU-stone group had inadequate stone presentation data because of radiolucent stones, the patients with AAU stones still had a significantly higher proportion of bladder stones (44% vs. 24%, respectively, \( p = 0.027 \)) and larger mean stone size (1.90 cm vs. 1.22 cm, respectively, \( p = 0.007 \)) than those with non-AAU stones. A UTI with a positive culture was noted in more than half of the patients (52%) in the AAU group and most of them had Proteus, Klebsiella, or Escherichia coli infections. Of those patients with AAU stones, 15 (60%) were diagnosed with chronic kidney disease (CKD), which was defined as a GFR of <60 ml/min. The AAU-stone group had a significantly higher proportion of patients with CKD (\( p = 0.001 \)), UTI with positive culture (\( p = 0.002 \)), IBS (\( p = 0.001 \)), and gout (\( p = 0.027 \)) than the non-AAU-stone group; however, there was no significant difference in laxative abuse between the two groups. Although the number of patients analyzed was small, there was a trend toward a higher incidence of urethelial carcinoma in the AAU-stone group than in the non-AAU-stone group (12% vs. 1.7%, respectively, \( p = 0.009 \)). Another interesting finding was the pH of the urine. We compared the pH of the urine from the patients with AAU, uric acid (243 cases), and struvite (magnesium ammonium phosphate; 25 cases) stones. The mean urine pH of the patients with AAU, uric acid, and struvite stones was 6.36 ± 0.47, 5.33 ± 0.30, and 7.22 ± 0.52, respectively, with a statistically significant difference between the groups (\( p < 0.0001 \)). The urine pH level of those with AAU stones was higher than that of the patients with uric acid stones and lower than that of those with struvite stones (Fig. 2).

Discussion

Urolithiasis with AAU crystals can be classified as endemic or sporadic. Endemic cases are still observed in developing countries, and AAU urolithiasis was frequently seen at the beginning of the 20th century, particularly bladder calculi in children [8]. Nutritional poor diets that are low in animal protein, calcium, and phosphate, but high in cereal, greatly contribute to relatively high levels of ammonium and urate ions, resulting in stone formation. Chronic
diarrhea, which has a high incidence in developing countries, also leads to a loss of water and ions, which is another major underlying factor for AAU crystallization [9]. In 1966, Hsu et al. [10] noted that 38 out of 45 children with urolithiasis in Taiwan had predominantly AAU stones. However, the incidence of AAU stones has been decreasing in most of the countries in the so-called "endemic bladder stone belt" with gradual improvements in nutrition levels and public health education. At present, sporadic cases of AAU urolithiasis are unusual in industrialized countries, and the prevalence varies with different geographical areas; e.g., 0.3% in the United States [5], 0.38% in Japan [11], 0.7% in our study, and up to 0.75% in Norway [12]. In contrast, there are still abnormally high incidences of AAU stones in specific regions. Vincent et al. reported that the prevalence of AAU-containing stones was as high as 3.1% in North America [4]. The apparent geographic variations indicate that genetic, dietary, and environmental factors may play important roles in the formation of AAU stones.

Due to the rare occurrence of AAU stones, only a few studies have reported their clinical and biochemical presentation, and the actual mechanism of AAU crystal formation has not been well established. According to previous pathophysiological evidence of urolithiasis

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**Figure 1.** Stone compositions analyzed by infrared spectrophotometry. The AAU stone leads to an increase in the intensities of the bands at 617, 707, 1005, 1386, 1429 and 1655, compared with increases in intensity for the calcium stone at 517, 780, 1316 and 1623. AAU = ammonium acid urate.
L. Urease can hydrolyze urea to ammonia and CO₂, and ammonia levels are maintained at approximately 100 mEq/L. Under physiological conditions, urinary ammonium and urate in the development of AAU formation are believed to involve multiple factors, a growing number of studies have identified the key roles of increased levels of urinary ammonium and urate, increased levels of urinary supersaturation-related crystallization, decreased inhibi-
tors of stone formation, and increased levels of urinary urate and ammonium. Although these mechanisms are believed to involve multiple factors, a growing number of studies have identified the key roles of increased levels of urinary ammonium and urate in the development of AAU urolithiasis. Under physiological conditions, urinary ammonia levels are maintained at approximately 100 mEq/L. Urease can hydrolyze urea to ammonia and CO₂, and bacterial urease, which is normally intracellular, is released into the urine after the lysis of bacterial cells. As a result, a UTI with urease-producing bacteria could increase the levels of urinary ammonium and lead to highly alkaline urine, both being preconditions for the formation of struvite and AAU crystals. In our study, more than half of the patients with AAU stones had a UTI, which was significantly higher than in the patients with non-AAU stones. Most of the detected pathogens were common urease-producing pathogens, such as Proteus, Klebsiella, Pseudomonas, and Staphylococcus. By contrast, a previous study indicated that patients with AAU and uric acid stones overproduce and overexcrete uric acid. Hyperuricemia and a purine-rich and phosphorus-poor diet combined with low fluid intake would not only give rise to gout attacks, but also promote the formation of highly concentrated uric acid, which forms ions and salts that are known as urates and acid urates, in urine. When excessive levels of ammonium combine with enough acid urates in urine, AAU crystals are produced. In this study, we observed significant associations between AAU stone formation and both UTIs and gout (p = 0.002 and 0.027, respectively).

Another important factor of AAU crystallization involves the solubility and stability of supersaturated ammonium and acid urate, which are strongly affected by the urinary pH level. Previous studies have demonstrated associations between urinary pH and various stones. The normal renal handling of urate is a complicated process resulting in a fractional clearance of 8.2% to 10.3%. Uric acid ionizes to form urate at pH 5.75, and uric acid solubility is strongly increased by urinary pH. Conversely, a lower urinary pH level increases the concentration of the sparingly soluble undissociated uric acid, which directly promotes the formation of uric acid stones. Struvite stone formation is highly correlated with urease-producing uropathogens and highly alkaline urine. Struvite only precipitates at a pH value of higher than 7.2. When urine is acidified, struvite can no longer precipitate and begins to dissolve. Bowyer et al. found that AAU crystals disappeared from urine with a pH value of <5.7 and that

<table>
<thead>
<tr>
<th>Stone presentation(^a)</th>
<th>AAU stones</th>
<th>Non-AAU stones</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single, n (%)</td>
<td>11 (44%)</td>
<td>1719 (50%)</td>
<td>0.544</td>
</tr>
<tr>
<td>Size (cm)</td>
<td>1.90 ± 1.31</td>
<td>1.22 ± 1.18</td>
<td>0.007</td>
</tr>
<tr>
<td>Bladder stone, n (%)</td>
<td>11 (44%)</td>
<td>828 (24%)</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Laboratory data

- **Serum uric acid (mg/dL)**: 7.00 ± 1.78 vs. 7.18 ± 2.01, p = 0.645
- **Serum calcium (mg/dL)**: 8.88 ± 0.60 vs. 8.76 ± 0.58, p = 0.301
- **Urinary pH**: 6.36 ± 0.47 vs. 6.26 ± 0.63, p = 0.427
- **CG-GFR (mL/min)**: 59.57 ± 26.56 vs. 78.64 ± 29.69, p = 0.002

Comorbidities

- **Chronic kidney disease, n (%)**: 15 (60%) vs. 892 (26%), p = 0.001
- **UTI with positive culture, n (%)**: 13 (52%) vs. 831 (24%), p = 0.002
- **Proteus**: 4 vs. 3
- **Klebsiella**: 3 vs. 2
- **Escherichia coli**: 3 vs. 2
- **Pseudomonas**: 2 vs. 2
- **Staphylococcus**: 1 vs. 2
- **Others**: 2 vs. 2

IBS, n (%)

- 9 (36%) vs. 446 (13%), p = 0.001

Laxative abuse, n (%)

- 7 (28%) vs. 1132 (33%), p = 0.597

Gout, n (%)

- 7 (28%) vs. 447 (13%), p = 0.027

Urothelium

- 3 (12%) vs. 57 (1.7%), p = 0.009

IBS = irritable bowel syndrome; UTI = urinary tract infection.

\(^a\) A total of 429 cases had inadequate data due to radiolucent stones on X-ray.

AAU = ammonium acid urate; CG-GFR = Cockcroft-Gault glomerular filtration rate; IBS = irritable bowel syndrome; UTI = urinary tract infection.

**Figure 2.** Correlation between urine pH and stone component. Vertical bars indicate mean ± SD. AAU = ammonium acid urate.
the minimum concentration of AAU crystals formed at pH values of between 6.2 and 6.3. Therefore, the urinary pH favoring AAU stone formation would be between that of struvite stones and uric acid stones, possibly because the urine of patients with AAU stones is supersaturated with ammonium and urate. This is consistent with our findings that showed the AAU-stone group had a similar mean urine pH level (pH = 6.36 ± 0.47). The patients with struvite stones had the highest mean urinary pH, while those with uric acid stones had the lowest level (Fig. 2).

Traditionally, AAU stones were considered to correlate with frequent diarrhea, laxative abuse, IBS, and anorexia nervosa [3,4,19,20]. Possible causes include a volume-depleted state and intracellular metabolic acidosis caused by the loss of water and electrolytes. A 24-hour urine study showed a marked decrease in volume, and sodium, citrate, and potassium levels in people abusing laxatives [21]. The aforementioned conditions is the volume depleated state and intracellular metabolic acidosis. Sobel et al. [5] reported that a history of inflammatory bowel disease or diverting ileostomy is a risk factor for AAU urolithiasis, and the plausible mechanism is similar to that for laxative abuse. In our study, IBS was significantly associated with AAU stone formation in univariate analysis (p = 0.001), but laxative abuse was not (p = 0.597). These results differ from those of other reports. We believe that insufficient numbers of patients and inadequate data collection during telephone interviews are two major factors contributing to these differences. The multiplicity of characteristics in our AAU patients also demonstrates that AAU crystal formation is the result of multiple factors.

However, we did observe some trends in the features of the patients in the AAU-stone group compared with those in the non-AAU-stone group. For example, AAU stones tended to be larger and had a higher incidence of forming in the bladder. There were also significantly more females and patients of an older age in the AAU-stone group than in the non-AAU-stone group. A plausible reason for these observations may lie in the relatively high prevalence of UTIs and asymptomatic bacteriuria in this group of patients. The prevalence of asymptomatic bacteriuria among healthy, community-residing women increases with advancing age, from about 1% among school girls to >20% among women aged >80 years [22]. Certain common physiological changes may also increase the likelihood of AAU stone formation. Loss of nephron mass is an important and predictable feature of aging that reduces the GFR by approximately 1 mL/min for every year over 40 years of age, and alterations in kidney function are more significant in aging females. In our study, there was also a significant reduction in GFR in the AAU-stone group compared with the non-AAU-stone group (59.57 vs. 78.64 mL/min, respectively, p = 0.002). Furthermore, 60% of patients in the AAU-stone group were affected by CKD with a Cockcroft-Gault-estimated GFR of <60 mL/min. Despite the fact that accumulating evidence has identified an association between urolithiasis and CKD [23], the precise etiology of this relationship has not been well established. Further studies are needed to evaluate the factors that underlie this association; e.g., whether alterations in ion and water excretion could contribute to the instability of AAU supersaturation or whether poor nutritional status could contribute to the high levels of ammonium and urate ions in urine.

Another particularly noteworthy finding in this study is the coexistence of AAU crystals and urothelial carcinoma. Urolithiasis has been considered to be a risk factor for urothelial carcinoma [24]. Although the exact mechanism has not been proven, it is thought to involve chronic inflammation and mucosal irritation that leads to urothelial proliferation and eventual malignant transformation. Notwithstanding the small number of patients studied, we found an abnormally high coexistence (12%) of AAU stones and urothelial carcinoma. This made us wonder whether components of AAU crystals caused urothelial carcinoma or if the cytokines involved in urothelial carcinoma caused AAU crystals. To elucidate the potential relationships between these two conditions, further large-scale pathological studies are clearly needed.

There were some limitations in our study. Firstly, we did not perform many of the available biochemical analyses of urine, e.g., calcium and uric acid level determination. The clinical presentation seemed to be inadequate for the accurate estimation of the risk factors of AAU stones. Secondly, AAU stones were not classified into pure and mixed types. The pathophysiological mechanisms of AAU urolithiasis may differ between the pure and mixed AAU types. Hidetoshi et al. [11] reported that 70.0% of patients with pure AAU stones engaged in laxative abuse compared with 26.3% of patients with mixed stones. Incomplete biochemical urine tests and inadequate classification data might lead to inaccurate risk stratification. The final limitations were that this study was retrospective and the number of AAU patients analyzed was small. In addition, variability in data collection during telephone interviews was also inevitable. To investigate the actual underlying correlation between the clinical characteristics and AAU stones, 24-hour urine samples and fasting blood samples are needed in further large-scale and well-distinguished prospective studies.

Summary

In conclusion, the clinical and biochemical presentation of patients with AAU urolithiasis included a female predominance, older age, more bladder presentations, larger size of stones, and a higher percentage of coexisting CKD, UTIs, IBS, gout, and urothelial carcinoma. A high proportion of patients with renal insufficiency were diagnosed in this study; therefore, in patients with AAU urolithiasis, it is important for clinicians to not only evaluate comorbid conditions but also to consider possible CKD and protect renal function, especially in females and those of relatively older ages.

References


