# Biochemical profile of idiopathic uric acid nephrolithiasis

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*Background.* The objective of this study was to elucidate a biochemical profile of patients with idiopathic uric acid nephrolithiasis, without secondary causes (such as dehydration or diarrhea). Study subjects comprised 56 patients with idiopathic uric acid nephrolithiasis (UA stone group) who underwent a full outpatient evaluation. The control group was composed of 54 with absorptive hypercalciuria and 2 normal subjects, matched with the UA stone group according to age, body mass index, and gender.

*Methods.* Urinary pH and ammonium and serum and urinary uric acid were measured. The fractional excretion of urate was calculated.

*Results.* Compared with the control group, the UA stone group had a significantly higher serum uric acid and significantly lower urinary uric acid, pH ($5.34 \pm 0.23$ vs. $6.17 \pm 0.36$, $P < 0.001$), and fractional excretion of urate ($0.052 \pm 0.028$ vs. $0.080 \pm 0.029$, $P < 0.001$), but individual values overlapped considerably between the two groups. Discriminant analysis of the relationship between urinary pH and fractional excretion of urate yielded a "discriminant score," which provided a much better separation between the two groups, with a correct classification in 95.5% of subjects. In contrast, urinary ammonium, citrate, sulfate, and potassium did not differ between two groups.

*Conclusions.* In idiopathic uric acid nephrolithiasis, urinary pH and fractional excretion of urate are significantly lower than in control subjects, suggestive of defects in urinary acidification and urate excretion. Since these impairments are believed to be associated with primary gout, the underlying disturbance in idiopathic uric acid nephrolithiasis may be primary gout.

Uric acid stones are known to form from dehydration, excessive sweating, intestinal alkali loss, and purine overload or overproduction. We previously described idiopathic uric acid nephrolithiasis, which develops in the absence of above secondary causes [1–3]. Requisite diagnostic features were uric acid stones occurring alone or with calcium oxalate stones associated with low urinary pH ($<5.5$), which cannot be explained by chronic diarrhea (intestinal alkali loss), strenuous physical exercise (lactic acidosis), or an unusually high animal protein diet (acid load) [2, 3]. This condition sometimes shared features of primary gout, including gouty arthritis, hyperuricemia, and hypertriglyceridemia [2]. Thus, we used the term "gouty diathesis" to describe this stone-forming entity [2, 3]. We had not regarded hyperuricemia as an essential diagnostic feature of gouty diathesis since some patients with primary gout, especially in the latent phase, may have normouricemia [4].

Unfortunately, the existence of this entity has not been widely accepted, in part due to incomplete diagnostic and pathophysiologic elucidation. The diagnostic criterion based mainly on urinary pH $<5.5$ [2, 3] may be insufficient. Depending on the acid-ash content of the diet consumed, urinary pH may not fall below 5.5 in some patients with uric acid nephrolithiasis, while it may be below this value in occasional nongouty subjects.

Moreover, the reliance on urinary pH failed to recognize the contribution of other presumed pathogenetic disturbances of primary gout. In primary gout, a defective renal ammoniagenesis is believed to be responsible for low urinary pH [4]. Another feature of primary gout is thought to be the enhanced net renal tubular reabsorption of uric acid [5, 6] that contributes to the development of hyperuricemia. The possible existence of these disturbances was not considered in our earlier diagnosis of gouty diathesis [2, 3].

This study was therefore conducted to search for the previously mentioned pathogenetic factors of primary gout and broaden diagnostic criteria of gouty diathesis. This task was undertaken by defining the biochemical profile of patients with idiopathic uric acid nephrolithiasis without secondary causes. From a retrospective analysis of data from stone-forming patients undergoing a full ambulatory evaluation [3], results obtained from 56 patients with uric acid stones were compared with those of the control group (without uric acid stones) matched according to age, body mass index (BMI), and gender. A special focus was placed on the comparison of urinary pH and measures of renal handling of uric acid.

## METHODS

### Patient data

Study subjects for this study were chosen from 2300 patients with stones and 68 normal subjects who had undergone our complete ambulatory evaluation [3] of nephrolithiasis from 1976 to 2000. Minimum diagnostic tests required were stone analysis, fasting venous blood chemistry, and stone risk analysis on a 24-hour urine sample collected during a "restricted" diet [3].

A total of 77 patients with uric acid stones verified by stone analysis were identified. Twenty-one patients were excluded because of incomplete data collection in 11 and secondary causes of uric acid stones or systemic disease in 10. The remaining 56 patients comprised the idiopathic uric acid nephrolithiasis group (UA stone group). Twenty-nine patients had "pure" uric acid stones, since only uric acid was identified on stone analysis. The remaining 27 patients had "mixed" stones, since they had stones containing both uric acid and calcium oxalate or formed both uric acid and calcium oxalate stones on separate occasions. None of the patients had chronic diarrheal state or high cell turnover or degradation. None gave a history of forming stones following strenuous physical exercise [7] or upon imposition of a high-protein diet for weight reduction or muscle building [8].

The control group was selected from a pool of 219 patients with absorptive hypercalciuria (AH) and 68 normal subjects who had undergone outpatient evaluation [3] since 1995. An attempt, with the aid of a computer, was first made to match the patients with AH with those of the UA stone group one-to-one, according to age (within 5 years), BMI (within 3 kg/m²), and gender (men or women). The pool of normal subjects was used for matching when the initial attempt in patients with AH was unsuccessful. When so selected, the control group comprised 54 patients with AH and 2 normal subjects. Patients with AH had calcium oxalate stones, normocalcemia, normal serum PTH, and exaggerated calciuric response to an oral calcium load (>0.2 mg calcium/mg creatinine) [3]. They did not have gouty arthritis or form uric acid stones. Normal subjects did not suffer from renal stones or gouty arthritis.

Endogenous creatinine clearance exceeded 0.6 mL/min/kg body weight in all participating subjects from both groups.

### Laboratory tests

From each subject, a 24-hour urine sample was collected after one-week of a high fluid intake (3 L/day) and adherence on an instructed diet restricted in calcium (400 mg/day), sodium (100 mEq/day), and oxalate [3]. On the morning after completion of urine collection, a venous blood sample was obtained in the fasting state before breakfast. During this dietary preparation, no one

**Table 1.** Demography and biochemical presentation

| | UA stone group | Control group |
|---|---|---|
| *N* patients | 56 | 56 |
| Gender *M/F* | 47/9 | 47/9 |
| BMI *kg/m²* | 30 ± 6 | 29 ± 5 |
| range | (21–48) | (10–45) |
| Age *years* | 49 ± 11 | 49 ± 11 |
| range | (28–72) | (30–68) |
| Biochemical presentation | | |
| Serum | | |
| Uric acid *mg/dL* | 7.1 ± 1.7[a] | 5.3 ± 1.1 |
| Triglycerides *mg/dL* | 173 ± 93 | 191 ± 163 |
| Urine | | |
| Uric acid *mg/day* | 545 ± 194[a] | 716 ± 243 |
| pH | 5.34 ± 0.23[a] | 6.17 ± 0.36 |
| Ammonium *mEq/day* | 36 ± 13 | 43 ± 20 |
| Citrate *mg/day* | 530 ± 319 | 532 ± 274 |
| Sulfate *mmol/day* | 25 ± 8 | 24 ± 10 |
| Sodium *mEq/day* | 160 ± 73 | 185 ± 100 |
| Potassium *mEq/day* | 52 ± 21 | 60 ± 18 |
| Fractional excretion of urate | 0.052 ± 0.028[a] | 0.080 ± 0.029 |
| Creatinine clearance *mL/min* | 115 ± 36 | 124 ± 32 |

BMI is body mass index.
Data are presented as mean ± SD.
Significance from control group is indicated: [a]$P < 0.001$

received drugs that could affect urate metabolism (such as allopurinol, high dose acetyl-salicylic acid) or supplements of calcium, alkali, magnesium, or phosphate. Participation in strenuous physical exercise was denied.

Serum samples were measured for uric acid, triglyceride, and creatinine, and urine samples were analyzed for uric acid, pH, ammonium, citrate, sulfate, sodium, potassium, and creatinine. Uric acid was analyzed by the uricase method, creatinine by the picric acid method, and ammonium by the glutamate dehydrogenase method. Urinary pH was measured with a pH electrode. Urinary assays were performed in fresh refrigerated samples. In rare samples in which uric acid had precipitated, the precipitate was dissolved in hot lithium hydroxide before the uric acid analysis.

### Statistical analysis

Endogenous uric acid clearance and creatinine clearance were calculated from values for uric acid and creatinine in 24-hour urine and fasting serum samples. The fractional excretion of urate was calculated as the ratio of uric acid clearance and the corresponding creatinine clearance.

The Shapiro-Wilks test was used to test normality of observations. Accordingly, either a *t* test or a Wilcoxon Rank Sum test was used to compare the results of the UA stone group with those of the control group. The Pearson product-moment correlation coefficient was computed for the relationship between urinary pH and fractional excretion of urate. Logistic regression was used to obtain a function (discriminant score), which discriminated between the two groups.
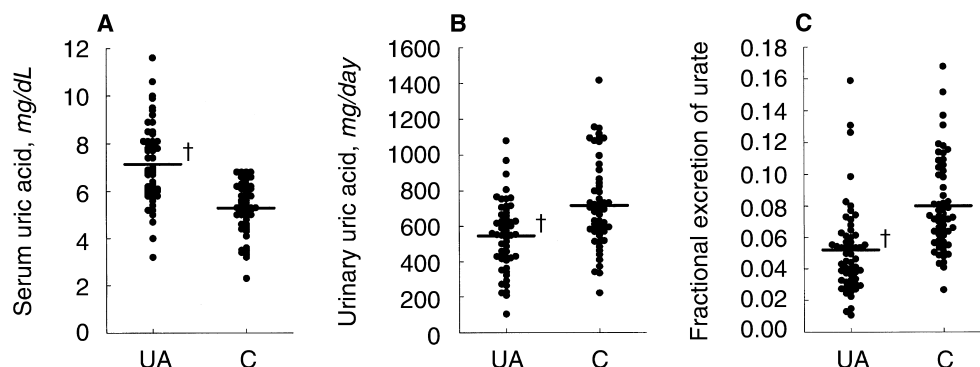
**Fig. 1. Individual display of serum uric acid (*A*), urinary uric acid (*B*) and fractional excretion of urate (*C*).** Horizontal bars indicate mean values. †*P* < 0.001 between the two groups. Abbreviations are: UA, idiopathic uric acid nephrolithiasis; C, control subjects.

## RESULTS

### Demographic presentation

Table 1 compares the demographic and biochemical features of the UA stone group with those of the control group. There was no significant difference in male–female distribution, BMI and age between the two groups. BMI ranged from 21 to 48 kg/m$^2$ with a mean value of 30 kg/m$^2$ in the UA stone group and 19 to 45 kg/m$^2$ with a mean of 29 kg/m$^2$ in the control group. Twenty-four patients from the UA stone group and 20 patients from the control group were obese or morbidly obese (BMI > 30 kg/m$^2$).

### Biochemical presentation

Serum uric acid was significantly higher in the UA stone group than in the control group (Fig. 1 and Table 1). The mean value approximated the upper limit of normal in the UA stone group (7 mg/dL), but was within normal limits in the control group. Conversely, urinary uric acid and fractional excretion of urate were significantly lower in the UA stone group than in the control group. Individual values for these three parameters overlapped considerably between the two groups (Fig. 1).

Urinary pH was significantly lower in the UA stone group than in the control group (Fig. 2, Table 1). Low urinary pH (<5.5) was disclosed in most patients from the UA stone group (43 of 56) and no one from the control group. Despite significant difference in mean values, a considerable overlap of individual values was found between the two groups with 11 points from the UA stone group residing within the range of the control group.

Urinary ammonium did not differ significantly between the two groups, even though the mean value was lower in the UA group (Fig. 2 and Table 1). Individual values overlapped extensively between the two groups with all points from the UA stone group residing within the range of the control group.

No significant difference was found between uric acid and control groups in serum triglyceride, urinary citrate, sulfate, sodium, potassium, and endogenous creatinine clearance (Table 1). Serum triglyceride was elevated (>150 mg/dL) in both groups.

Biochemical presentation of 29 patients with pure uric acid stones did not differ from those of 27 patients with mixed stones of uric acid and calcium oxalate. Thus, urinary pH was 5.33 ± 0.18 in the pure group compared with 5.35 ± 0.28 in the mixed group.

### Dependence of fractional excretion of urate on urinary pH

The relationship between urinary pH and fractional excretion of urate is shown in Figure 3. Most of the points from the UA stone group resided in the left lower half of the plot. Most of the points from the control group were located in the right upper half. The sample correlation coefficient was 0.39 (*P* < 0.01). Logistic regression to discriminate the two groups yielded the line shown in Figure 3.

From the preceding analysis, a discriminant function ("discriminant score" or DS) was obtained as a linear equation: DS = 13.6 (pH) + 45.7 (fractional excretion of urate). Thus, for a given patient, the discriminant score could be calculated by simply multiplying pH by 13.6 and fractional excretion of urate by 45.7, and then adding the two products. Discriminant scores for members of the two groups are individually displayed in Figure 4. The discriminant score of 80 separated the two groups. A given subject with a score ≥80 would be normal, and a value <80 would be uric acid stones. Accordingly, only two patients in the UA stone group (3.6%) were misclassified as normal, and only three subjects in the control group (5.4%) were misclassified as uric acid stones. Thus, the correct classification was obtained in 96.4% of uric acid stone group, 94.6% of the control group, and 95.5% overall. These percentages are probably optimistic estimates, since the same sample was used to develop the score and derive the classification.
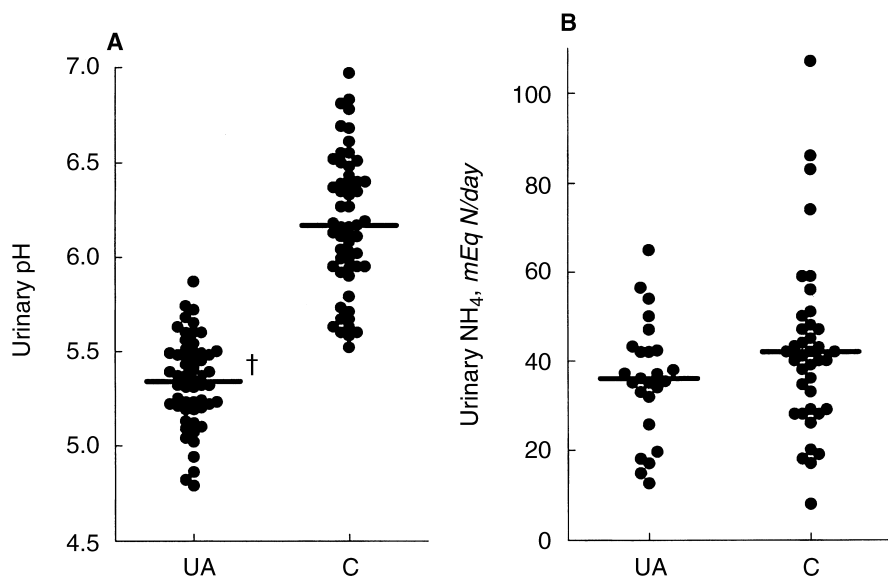
**A**

**B**

**Fig. 2. Individual display of urinary pH (*A*) and urinary ammonium (*B*).** †$P < 0.001$.
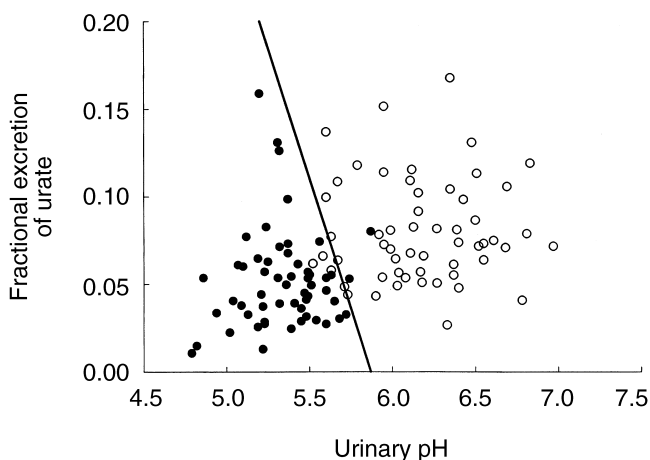


**Fig. 3. Relationship of urinary pH and fractional excretion of urate.** The diagonal line indicates the discriminant line obtained by logistic regression.
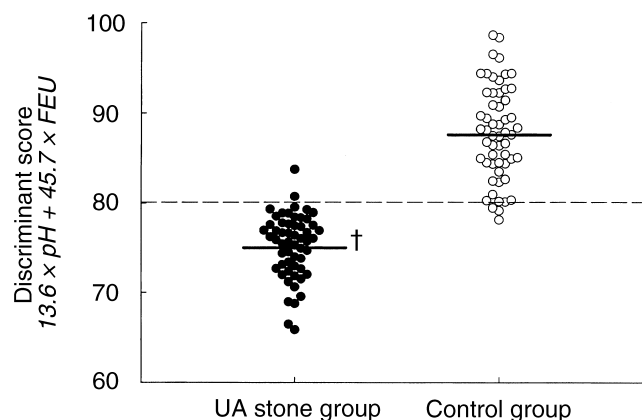
**Fig. 4. Discriminant score of the relationship between urinary pH and fractional excretion of urate (FEU) in the (●) idiopathic uric acid nephrolithiasis group and (○) control group.** The horizontal dashed line indicates discriminant score of 80 that separated the two groups. †$P < 0.001$.

## DISCUSSION

This study was undertaken to characterize the biochemical presentation of patients with idiopathic uric acid nephrolithiasis without secondary causes. Compared with the control group, the UA stone group had a significantly lower urinary pH and urinary uric acid, and significantly higher serum uric acid ($P < 0.001$). Urinary ammonium did not differ significantly between the two groups. The logistic regression of the relationship between urinary pH and fractional excretion of urate yielded discriminant score, with a value <80 in most patients with uric acid stones and ≥ 80 in most control subjects.

Considerable care was taken in the selection of study subjects. Only patients with documented uric acid nephrolithiasis were selected. None of the patients had evi-

dence for secondary causes of uric acid nephrolithiasis. Moreover, the patients in the control group were carefully selected so they would match the UA stone group according to age, BMI, and gender. A high BMI may cause insulin resistance [9], which may then influence urinary pH and urate excretion [10]. Thus, it was important to match the control subjects to the test population with respect to BMI.

In an earlier report, hypertriglyceridemia was frequently found among patients with gouty diathesis with uric acid stones [2]. In this report, a high serum triglyceride was disclosed in both the UA stone group and the control group. Thus, this biochemical abnormality is probably a feature of obesity.

However, the UA stone group could be distinguished from the control group in disclosing a significantly lower

urinary pH, as reported in the earlier description of gouty diathesis [2, 3]. This finding probably is not due to varying acid-ash content of the diet. The two groups had similar values for urinary citrate (measure of acid-base status), sulfate (marker for dietary intake of sulfur-containing amino acids), and potassium (index of potassium alkali ingestion). The exact cause for low urinary pH in UA stone group remains unknown.

Besides lower urinary pH, the UA stone group had a significantly higher serum uric acid and significantly lower urinary uric acid than the control group. Fractional excretion of urate, which incorporated the contribution of both serum and urinary uric acid, was significantly lower in the UA stone group. This finding cannot be explained by animal protein excess since oral purine load increases both serum and urinary uric acid [11].

We suggest that the above biochemical features of UA stone group may be unique, possibly reflective of pathophysiologic disturbances of underlying primary gout. In primary gout, urinary pH is low, causing uric acid stones [4, 5]. The fractional excretion of urate is reduced, contributing to the development of hyperuricemia and gouty arthritis [5]. Prior reports have suggested that the cause of low urinary pH in primary gout may be defective renal ammoniagenesis [4]. In this study, urinary ammonium of the UA stone group did not differ significantly from the control group, even though the mean value was lower in the former group. However, since urinary ammonium had been measured on 24-hour urine specimens, various dietary factors could have influenced ammonium excretion. While fasting urine samples would have been more desirable to discern alleged impairment in renal ammoniagenesis, we had not measured urinary ammonium in fasting samples.

The alleged disturbances of primary gout may not be present in all patients. Thus, some but not all patients with primary gout suffer from uric acid stones or gouty arthritis or display hyperuricemia at a given time [2, 4]. Despite significant differences in mean values, values for urinary pH and fractional excretion of urate from the UA stone group overlapped considerably with those of the control group, with some patients with uric acid stones enjoying normal values.

A much better separation of the gouty diathesis group from the control group was possible from discriminant analysis employing urinary pH and fractional excretion of urate as variables. A regression line could be constructed that provided a correct classification of UA stone group or the control group in 96% of subjects. Thus, either a low urinary pH or low fractional excretion of urate was present in the vast majority of patients in the UA stone group, whereas each defect alone was encountered in some but not all patients.

The disclosure of an apparent impairment in urinary acidification and urate excretion in the test population apart from the matched control group suggested that these disturbances are metabolic or genetic in origin and are not acquired. Thus, the prior use of the term gouty diathesis [2, 3] to describe idiopathic uric acid nephrolithiasis may be justified. Moreover, the discriminant score classifying UA stone group from the control group may have a diagnostic value in identifying patients with gouty diathesis. A further refinement of this relationship may yield a phenotypic marker that may be useful in molecular genetic elucidation of gouty diathesis.

In summary, stone-forming patients with idiopathic uric acid nephrolithiasis were shown to have biochemical features of primary gout, characterized by low urinary pH and fractional excretion of urate. Thus, idiopathic uric acid nephrolithiasis may represent a stone manifestation of primary gout. The biochemical presentation presented here should be useful in the detection of patients with idiopathic uric acid nephrolithiasis.

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