

# Spot Urine Uric Acid to Creatinine Ratio Used in the Estimation of Uric Acid Excretion in Primary Gout

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**ABSTRACT. Objective.** Uric acid overexcretion in patients with gout is frequently assessed by the measurement of 24 hour urinary uric acid excretion, which is cumbersome with ambulatory patients, and requires accurate timing and complete collection of the specimen. We assessed whether uric acid to creatinine ratio (Uua/Ucr) in spot urine is useful for the estimation of uric acid overexcretion in patients with gout.

**Methods.** One hundred thirty male patients with gout and 33 non-gout male control subjects were studied. Early morning urine and/or a portion of 24 h collected urine (24 h urine) were used as spot urine samples. Uric acid overexcretors were defined as those with a 24 h urinary uric acid excretion  $\geq 1000$  mg/day, while uric acid underexcretors were defined as those with uric acid clearance  $< 6$  ml/min.

**Results.** There was a significant relationship between 24 h urinary uric acid excretion and early morning urine Uua/Ucr in patients with gout, while no such relationship was observed in controls. No significant difference in Uua/Ucr was observed between patients with gout and controls, or in Uua/Ucr between gout uric acid overexcretors and underexcretors in early morning urine. A significant difference in this value was observed between the 2 groups in the 24 h urine specimens. Although the diagnostic accuracy of gout uric acid overexcretion was 87.2% using early morning urine and 89.6% using 24 h urine, the sensitivity of gout uric acid overexcretion was only 25.0% when using early morning urine and 25.0% when using 24 h urine, when the cutoff value of Uua/Ucr was 0.63 and 0.64, respectively.

**Conclusion.** Uua/Ucr using spot urine, especially early morning urine, is not an accurate indicator of uric acid overexcretion in patients with gout. (J Rheumatol 2001;28:1306–10)

## Key Indexing Terms:

URIC ACID EXCRETION SPOT URINE URIC ACID TO CREATININE RATIO GOUT

Uric acid overexcretion in patients with gout is frequently assessed by the measurement of 24 hour urinary uric acid excretion. However, 24 h urine collection is cumbersome with ambulatory patients, and requires accurate timing and complete collection of the specimen. To overcome these drawbacks, some investigators have suggested that the uric acid to creatinine ratio (Uua/Ucr) in spot urine is an acceptable indicator of uric acid overexcretion<sup>1,2</sup>, while others have suggested that it is not<sup>3</sup>. We assessed whether Uua/Ucr in spot urine is useful for the estimation of uric acid overexcretion in patients with primary gout.

## MATERIALS AND METHODS

One hundred thirty male patients with gout (underexcretion type: 95

patients, mixed type: 5, overexcretion type: 16, normoexcretion type: 14; mean age 49.3 yrs) and 33 non-gout healthy male control subjects (underexcretion type: 9 patients, mixed type: 0, overexcretion type: 5, normoexcretion type: 19; mean age 45.5 yrs) were included in our study. The diagnosis of primary gout was based on criteria outlined by the American Rheumatism Association<sup>4</sup>. The study was performed on an outpatient basis with no dietary restriction (daily purine intake, 150 to 250 mg), except for total abstinence from alcoholic beverages during the urine collection portion. However, all medications that might affect uric acid metabolism were withdrawn at least one month prior to the study. Early morning urine after overnight fast (early morning urine) and/or a portion of 24 h collected urine (24 h urine) were used as spot urine samples. Uric acid overexcretors were defined as those with a 24 h urinary uric acid excretion  $\geq 1000$  mg/day<sup>5</sup> with regular diet, while uric acid underexcretors were defined as those with a uric acid clearance  $< 6$  ml/min<sup>6</sup>.

The relationships between early morning urine Uua/Ucr and 24 h urinary uric acid excretion and the differences in Uua/Ucr values between patients with gout and control subjects were examined, as were gout patient uric acid overexcretors versus underexcretors. Sensitivity, specificity, and diagnostic accuracy of the estimation of uric acid overexcretion by spot urine Uua/Ucr were calculated by true positive/true positive + false negative, true negative/true negative + false positive, and true positive + true negative/total results, respectively. However, mixed type gout was excluded when determining sensitivity, specificity, and diagnostic accuracy.

Further, the effect of food intake (nutrients: calories, 838 Cal; protein, 44.9 g; fat, 24.8 g; carbohydrate, 100.6 g; NaCl, 8.1 g; K, 1057 mg; purine, 78.8 mg) on Uua/Ucr was examined in 5 healthy subjects. The protocol was

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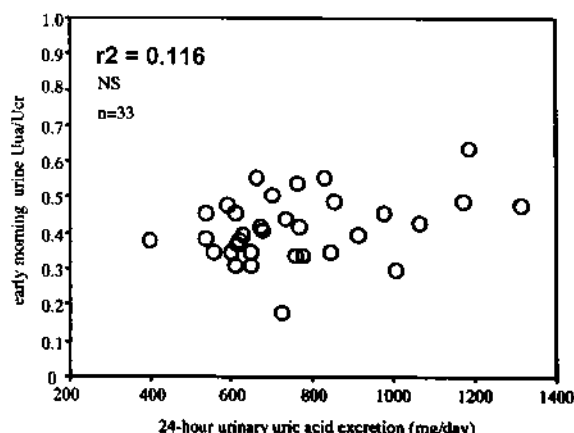
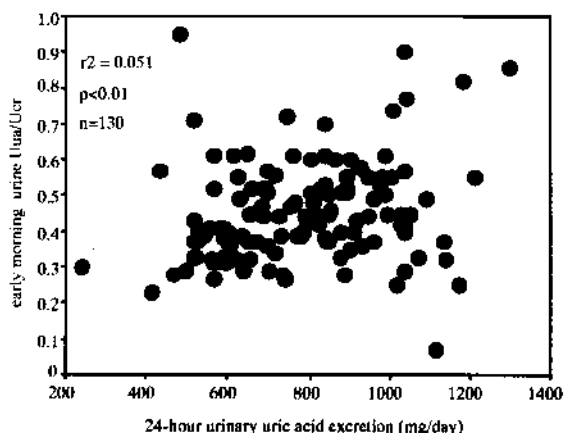
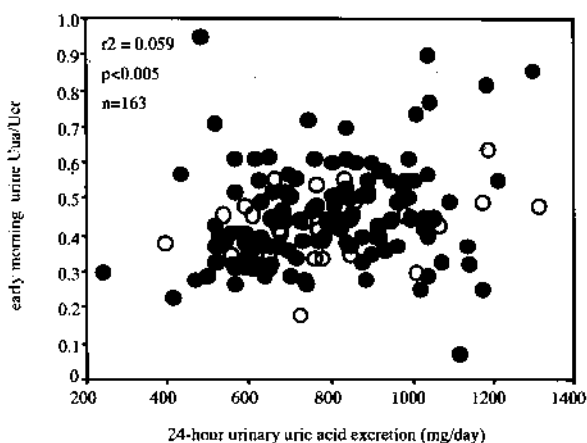
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as follows. After overnight fast, urine was completely voided. Next, urine was collected for 1 hour (urine 1), after which a test meal was ingested. Urine was then collected for 2 successive hours (urine 2, urine 3) and blood was drawn at the midpoint of each of these urine collection hours. Urine uric acid and creatinine concentrations were measured by a uricase method and Jaffe reaction, respectively, using commercially available kits (Uric acid B-test, Creatinine-test, Wako Pure Chemical Industries, Osaka, Japan). Uua/Ucr and the fractional clearance of uric acid (uric acid clearance/creatinine clearance  $\times 100$ ) were calculated.

The correlation between 2 variables was assessed by simple regression analysis. The observed differences between 2 groups and among all groups were assessed by unpaired 2 tailed Student's t test and one way analysis of variance, respectively. All calculations were performed using the Statview 4.5 statistical program (Abacus Concepts, Berkeley, CA, USA). P values below 0.05 were considered statistically significant.

## RESULTS

**Relationship between early morning urine Uua/Ucr and 24 hour urinary uric acid excretion.** There was a significant correlation between early morning urine Uua/Ucr and 24 h urinary uric acid excretion in all subjects (gout patients + controls) ( $p < 0.005$ ) (Figure 1, upper panel). However, this relationship was not observed when gout patients and controls were examined separately, as it was observed only in patients with gout (Figure 1, lower panel). The correlation coefficient was 0.23 in gout patients ( $p < 0.01$ ), while it was 0.34 in controls ( $p = 0.053$ ).



**Uua/Ucr between patients and controls, and in gout uric acid excretion type.** No significant differences in Uua/Ucr were observed between gout patients and controls ( $0.453 \pm 0.140$  vs  $0.417 \pm 0.092$  in early morning urine, Figure 2, left;  $0.479 \pm 0.095$  vs  $0.450 \pm 0.091$  in 24 h urine, Figure 2, right). In addition, there were no significant differences in early morning urine Uua/Ucr among gout patients (underexcreters,  $0.441 \pm 0.121$ ; mixed type,  $0.474 \pm 0.249$ ; overexcreters,  $0.493 \pm 0.222$ ; normoexcreters,  $0.482 \pm 0.086$ , Figure 3, left). However, there were significant differences among gout patient overexcreters, underexcreters, and normoexcreters for 24 h urine Uua/Ucr (overexcreters vs underexcreters,  $0.596 \pm 0.100$  vs  $0.450 \pm 0.078$ ,  $p < 0.01$ ; overexcreters vs normoexcreters,  $0.596 \pm 0.100$  vs  $0.522 \pm 0.068$ ,  $p < 0.05$ ). Moreover, 24 h urine Uua/Ucr in underexcreters was significantly lower compared with mixed type and normoexcreters ( $0.450 \pm 0.078$  vs  $0.532 \pm 0.085$ ,  $p < 0.05$ ;  $0.450 \pm 0.078$  vs  $0.522 \pm 0.068$ ,  $p < 0.01$ ) (Figure 3, right). As indicated in Table 1, the diagnostic accuracy of uric acid overexcreters was 87.2% using early morning urine and 89.6% using 24 h urine, when the cutoff value of Uua/Ucr was set at mean + 2 SD of the value (0.63 for early morning urine and 0.64 for 24 h urine) from subjects with normal uric acid excretion ( $C_{ua} \geq 6$  ml/min and 24 h uric acid excretion  $< 1000$  mg).

Figure 1. Relationship between early morning urine uric acid to creatinine ratio (Uua/Ucr) and 24 h urinary uric acid excretion in all subjects ( $n = 163$ ). There was a significant correlation between early morning urine Uua/Ucr and 24 h urinary uric acid excretion in all (gout patients + controls) ( $r = 0.24$ ,  $p < 0.005$ ) (upper panel); however, this relationship was not observed when patients ( $n = 130$ ) and controls ( $n = 33$ ) were examined separately. Further, this relationship was observed in patients (lower panel, left) but not in controls (lower panel, right). The correlation coefficient was 0.23 in patients ( $p < 0.01$ ), while it was 0.34 in controls ( $p = 0.053$ ). ●: patients with gout; ○: controls.

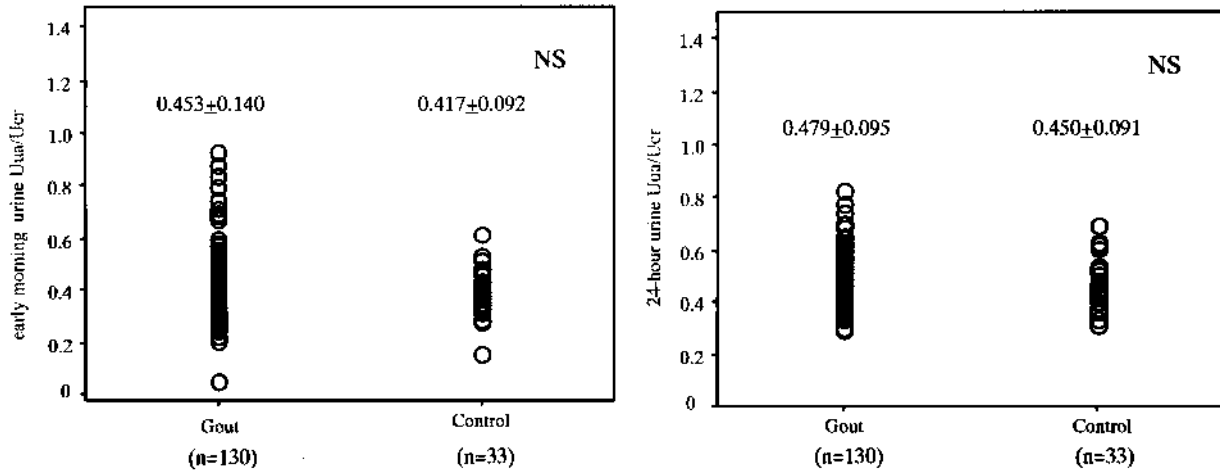


Figure 2. Relationship of early morning urine (left panel) and 24 h urine (right panel) uric acid to creatinine ratio (Uua/Ucr) between patients and controls. No significant differences in Uua/Ucr were observed between patients and controls ( $0.453 \pm 0.140$  vs  $0.417 \pm 0.092$  in early morning urine,  $0.479 \pm 0.095$  vs  $0.450 \pm 0.091$  in 24 h urine, respectively).

*Effect of a meal on Uua/Ucr in 5 healthy subjects.* Urinary excretions of uric acid, creatinine, Uua/Ucr, and fractional uric acid clearance increased significantly after 5 healthy subjects ingested a meal, compared with respective control values (Table 2). The increase in urinary excretion of uric acid exceeded that of creatinine, resulting in a significant increase in Uua/Ucr after the meal.

## DISCUSSION

Patients with gout are classified into uric acid overexcretion, underexcretion, and mixed type according to their uric acid metabolism derangement. These types are usually determined by the measurement of 24 h urinary uric acid excretion and uric acid clearance. However, 24 h urine collection and the measurement of uric acid clearance are cumbersome

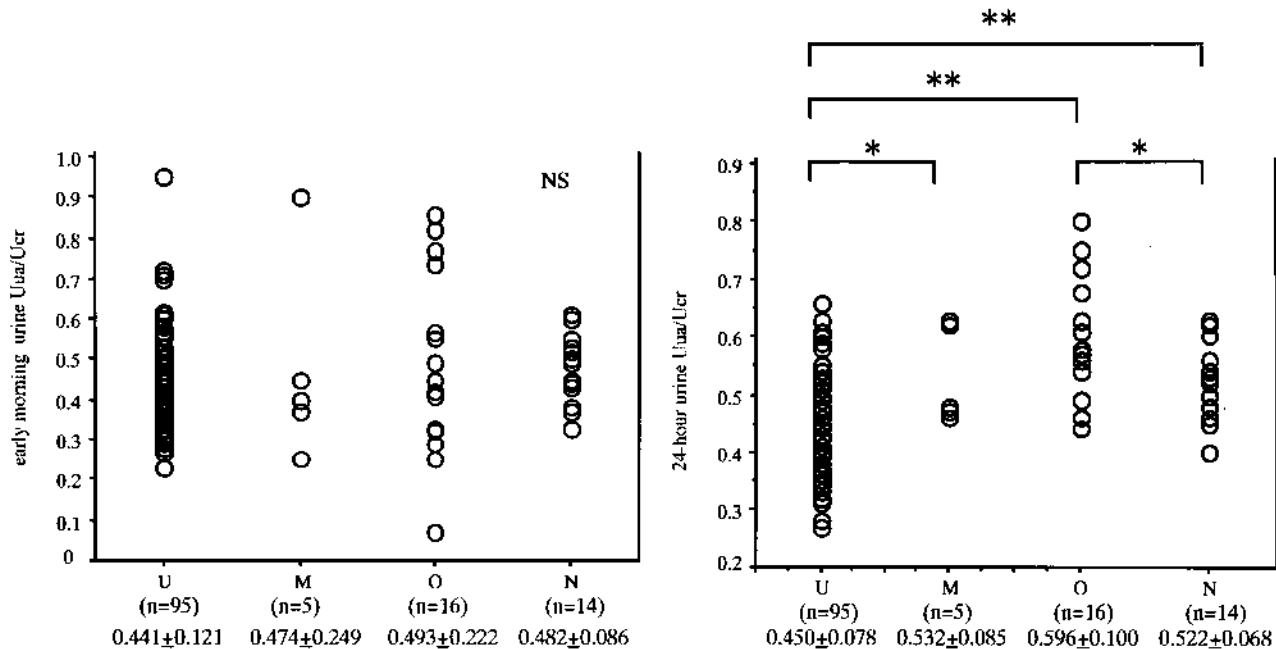


Figure 3. Relationship of early morning urine (left panel) and 24 h urine (right panel) uric acid to creatinine ratio (Uua/Ucr) among uric acid excretion type patients. No significant differences were observed in early morning urine Uua/Ucr among patients (underexcretors,  $0.441 \pm 0.121$ ; mixed type,  $0.474 \pm 0.249$ ; overexcretors,  $0.493 \pm 0.222$ ; normoexcretors,  $0.482 \pm 0.086$ ) (left panel). In contrast, there were significant differences in 24 h urine Uua/Ucr between patient uric acid overexcretors and underexcretors ( $0.596 \pm 0.100$  vs  $0.450 \pm 0.078$ ,  $p < 0.01$ ) and between overexcretors and normoexcretors ( $0.596 \pm 0.100$  vs  $0.522 \pm 0.068$ ,  $p < 0.05$ ). Moreover, 24 h urine Uua/Ucr in underexcretors was significantly lower compared with mixed type and normoexcretors ( $0.450 \pm 0.078$  vs  $0.532 \pm 0.085$ ,  $p < 0.05$ ;  $0.450 \pm 0.078$  vs  $0.522 \pm 0.068$ ,  $p < 0.01$ ) (right panel). U: underexcretion type; M: mixed type; O: overexcretion type; N: normoexcretion type.

Table 1. Sensitivity, specificity, and diagnostic accuracy of Uua/Ucr in the diagnosis of uric acid overexcretors.

Uua/Ucr	Sensitivity, %	Specificity, %	Diagnostic Accuracy, %
Early morning urine	25.0	96.3	87.2
24 hour urine	25.0	99.1	89.6

The cutoff value was settled at mean + 2 SD of Uua/Ucr in subjects with normal uric acid excretion (n = 33; 0.63 for early morning urine and 0.64 for 24 h urine).

with ambulatory patients, and require accurate timing and complete collection of the specimen. Urinary uric acid overexcretion has also been predicted from spot urine Uua/Ucr<sup>1,2</sup>. In certain enzymatic disorders, such as PRPP synthetase superactivity and hypoxanthine guanine phosphoribosyl transferase deficiency, a raised urine uric acid to creatinine ratio above 0.75 can be observed, suggesting the usefulness of spot urine Uua/Ucr in estimating uric acid overexcretion<sup>3</sup>. Therefore, we investigated the usefulness of Uua/Ucr in spot urine for the prediction of uric acid excretion in primary gout. In normal uric acid excretors (Cua  $\geq$  6 ml/min and 24 h urinary excretion of uric acid < 1000 mg), the mean  $\pm$  SD value of Uua/Ucr was  $0.445 \pm 0.094$  for early morning urine and  $0.475 \pm 0.083$  for 24 h urine. We defined overexcretion of uric acid as Uua/Ucr measurements > 0.63 for early morning urine and > 0.64 for 24 h urine, which are 2 SD above the respective means. Using these cutoff values, the sensitivity, specificity, and diagnostic accuracy of uric acid overexcretion were 25.0%, 96.3%, and 87.2% for early morning urine, and 25.0%, 99.1%, and 89.6% for 24 h urine. These cutoff values were rather low compared with those of Wortmann, *et al* (0.75)<sup>3</sup>. However, in our study using patients with primary gout we failed to demonstrate the usefulness of Uua/Ucr in the estimation of uric acid overexcretion since the sensitivity was extremely low. Yamanaka, *et al*<sup>7</sup> suggested a value of 0.5 for spot urine Uua/Ucr when diagnosing uric acid overexcretion in gout patients. The difference in results may be partly derived from the cutoff

Table 2. Changes in urinary excretions of uric acid, creatinine, uric acid to creatinine ratio (Uua/Ucr) and fractional uric acid clearance after ingestion of the test meal (n = 5).

	(1)	(2)	(3)
Uua (mg/h)	39.8 $\pm$ 6.7	50.4 $\pm$ 13.7	75.2 $\pm$ 17.4*
Ucr (mg/h)	110.5 $\pm$ 22.6	120.7 $\pm$ 28.3 <sup>#</sup>	129.4 $\pm$ 27.9*
Uua/Ucr	0.37 $\pm$ 0.08	0.42 $\pm$ 0.08	0.59 $\pm$ 0.12*
Cua/Ccr (%)	6.5 $\pm$ 2.5	6.9 $\pm$ 2.3	9.4 $\pm$ 2.8*

(1): 1 hour period before meal; (2): 0–1 hour period after meal; (3): 1–2 hour period after meal.

Cua/Ccr denotes fractional uric acid clearance (uric acid clearance/creatinine clearance  $\times$  100).

\* p < 0.01; <sup>#</sup>: p < 0.05, vs corresponding baseline values.

values used in the 2 studies, the value in our study being higher than that used by Yamanaka, *et al*. Moreover, in the study by Yamanaka, *et al* the definition of spot urine was obscure and their diagnostic accuracy results were not described. In our study, when using a cutoff value of 0.5 the diagnostic value of spot urine Uua/Ucr was not improved (early morning urine: sensitivity 43.8%, specificity 66.1%, diagnostic accuracy 63.2%; 24 h urine: sensitivity 81.3%, specificity 65.1%, diagnostic accuracy 67.2%). Simkin, *et al*<sup>8</sup> proposed that the product of urinary uric acid and serum creatinine concentrations divided by urinary creatinine concentration could be useful, using a cutoff value of 0.7 mg/dl, three SD above normal, in the estimation of uric acid excretion. However, as the serum creatinine concentration in their study was near 1.0, the actual results may not be significantly different.

The relationship of circadian rhythm and urinary uric acid concentration has been reported by several investigators<sup>9,10</sup>. The highest uric acid concentration in healthy subjects has been found between 5 AM and 8 AM, and the lowest between 11 PM and 2 AM<sup>9</sup>. Similarly, a chronobiological variation in urinary creatinine excretion has been described<sup>11,12</sup>. Therefore, Uua/Ucr seems to be controlled by circadian rhythm. Moreover, Uua/Ucr is considered to be affected by several exogenous factors such as feeding habits, urine volume, and physical activity. Among them, food intake is likely to play a major role in affecting urinary uric acid concentration and/or excretion. As indicated in Table 2, in our study fractional uric acid clearance and Uua/Ucr both increased significantly after a meal. This phenomenon may be ascribable to the uricosuric action effect of protein<sup>13</sup>, in addition to the nucleoprotein that was contained in the test meal. Therefore, physicians should be cautious in interpreting Uua/Ucr as an indicator of uric acid excretion, and the effect of food ingestion should be taken into consideration. Accordingly, the definition of spot urine must be clarified when using this simple variable as a tool for estimating uric acid excretion. Early morning urine has been suggested to show a good reproducibility with Uua/Ucr in the same individual<sup>1</sup>. However, in our study, Uua/Ucr in early morning urine showed a poor correlation to 24 h urinary excretion of uric acid in control subjects and had a low diagnostic accuracy. Therefore, early morning spot urine Uua/Ucr is not an accurate indicator of uric acid excretion in patients with primary gout.

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