The Inflammatory Process in the Mechanism of Decreased Serum Uric Acid Concentrations During Acute Gouty Arthritis

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ABSTRACT. ***Objective.*** To clarify the mechanism of decreased serum uric acid (SUA) concentrations during acute gouty arthritis.

Methods. Data from patients with acute gouty arthritis during and after an attack were investigated retrospectively. Other investigations, including changes in urinary excretion and biochemical markers, were performed prospectively.

Results. SUA was significantly lower in the acute phase (7.5 ± 1.4 mg/dl) than in the intercritical phase (8.5 ± 0.9 mg/dl) ($p < 0.0001$). During the acute gout phase, a normal SUA level was found in 20 of 41 patients (49%). C-reactive protein (CRP) during acute attacks was significantly correlated with plasma interleukin 6 (IL-6) and cortisol ($r = 0.645$, $p < 0.005$; $r = 0.460$, $p < 0.05$). Percentage change in SUA at onset of attack correlated with CRP and IL-6 ($r = 0.762$, $p < 0.0001$; $r = 0.630$, $p < 0.005$), as well as with increased urinary excretion of uric acid, estimated by percentage change in fractional excretion of uric acid (FEua) during attack ($r = 0.447$, $p < 0.05$). Further, change in FEua was correlated with plasma cortisol levels during the acute attack ($r = 0.534$, $p < 0.05$).

Conclusion. Decrease in SUA during acute gouty arthritis is associated with increased urinary excretion of uric acid; an inflammatory process may play a role in the mechanism. (J Rheumatol 2002;29:1950–3)

Key Indexing Terms:

GOUTY ARTHRITIS | INTERLEUKIN 6 | C-REACTIVE PROTEIN
CORTISOL | URIC ACID | URICOSURIC

Hyperuricemia is not only the causative condition in the pathogenesis of gout, but is also a useful marker for its diagnosis. Hyperuricemia has been reported to be closely linked to the risk of gouty arthritis[1]; thus the criteria for diagnosis of primary gout include hyperuricemia as an essential biochemical measurement[2]. In exceptional situations, gouty arthritis can develop in individuals with no history of hyperuricemia[3]. However, serum uric acid (SUA) level is sometimes within normal range during acute gouty attacks in patients who have been diagnosed with hyperuricemia. This phenomenon has become widely recognized[4], and caution has been advocated since this condition could be a diagnostic pitfall in the correct diagnosis of gout. Logan, *et al*[5] reported a longitudinal study on decreased SUA levels at the onset of gout attack. Thus, although it is obvious that SUA can decrease during acute gouty arthritis, neither the mechanism responsible for this phenomenon nor the precise situations in which SUA decreases have been clarified.

We investigated whether decreased SUA levels during gouty arthritis were associated with increased clearance of uric acid into urine, and whether the inflammatory process of acute gouty arthritis played a role in the mechanism responsible for this phenomenon.

MATERIALS AND METHODS

Patients. Data from patients with acute gouty arthritis during and after an attack were investigated retrospectively in this study. Of the patients with acute gouty arthritis who visited the Institute of Rheumatology from 1986 through 1998, 20 were selected for this analysis under the following conditions. Selected patients met the diagnostic criteria for acute gouty arthritis[2]; had not taken urate lowering agents including allopurinol, probenecid, and benzbromarone; and had had blood samples taken at 2 different times (during acute arthritis and within 2 weeks after the first visit).

To analyze relationships between change in uric acid, urinary excretion of uric acid, and biochemical markers, 21 patients who visited from 1998 through 1999 were selected using the same criteria and were followed prospectively. The 41 study patients (30–72 yrs, mean ± SD 48.5 ± 12.2) were all men with monoarticular arthritis. After informed consent had been

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obtained in prospective cases, patients enrolled in this analysis were treated mainly with nonsteroidal antiinflammatory drugs (NSAID). In cases of severe inflammation, use of corticosteroid was permitted.

Methods. SUA and C-reactive protein (CRP) levels were measured in all patients during and after an attack. For further study, uric acid and creatinine levels in serum and urine, serum CRP, and interleukin 6 (IL-6), cortisol and adrenocorticotropin hormone (ACTH) in plasma were measured at these 2 points in 21 patients. Urinary samples were spot urine, obtained at the patient's visit to the hospital. These patients were instructed to avoid any intake of alcoholic beverages until their next visit to the hospital. As indices to estimate urinary uric acid excretion, fractional excretion of uric acid (FEua) and excretion rate (ER) per unit glomerular filtration rate were calculated based on the serum and urinary levels of uric acid and creatinine. FEua represents uric acid clearance per creatinine clearance, and can be calculated as (urinary uric acid/SUA) × (serum creatinine/urinary creatinine). Similarly, ER can be calculated as (urinary uric × serum creatinine)/urinary creatinine[6,7]. The changes in SUA or uric acid excretion are shown as percentage change in SUA, FEua, and ER, respectively. These indices were calculated using the following formulas:

Percentage change in SUA:

$$\frac{(\text{serum UA2} - \text{serum UA1}) \times 100}{\text{serum UA1}}$$

Percentage change in FEua:

$$\frac{[(\text{urinary UA1/serum UA1})/(\text{urinary Cre1/serum Cre1}) - (\text{urinary UA2/serum UA2})/(\text{urinary Cre2/serum Cre2})] \times 100}{(\text{urinary UA1/serum UA1})/(\text{urinary Cre1/serum Cre1})}$$

Percentage change in ER:

$$\frac{[(\text{urinary UA1} \times \text{serum Cre1/urinary Cre1}) - (\text{urinary UA2} \times \text{serum Cre2/urinary Cre2})] \times 100}{(\text{urinary UA1} \times \text{serum Cre1/urinary Cre1})}$$

Plasma IL-6 concentrations were measured by ELISA kit (R&D Systems, Minneapolis, MN, USA).

Statistical analysis. Data are presented as mean ± 1 SD. Statistical analysis was performed using the Wilcoxon signed-ranks test for comparison of differences between the data for each pair, and the Mann-Whitney U test for comparing 2 independent groups of patients. Pearson's correlation coefficient was calculated to examine correlations between variables.

RESULTS

As shown in Table 1 and Figure 1, the mean levels of SUA in these patients during the acute gout phase (7.5 ± 1.4 mg/dl) were significantly lower than those in the intercritical phase (8.5 ± 0.9 mg/dl; $p < 0.0001$). The upper limit of the normal range of SUA in our laboratory is 7.5 mg/dl for men. Thus, during the acute gout phase, a normal SUA level was found in 20 of 41 patients (49%). Both CRP and IL-6, which are markers for acute inflammation, were significantly elevated in the acute gout phase.

We stratified these patients by CRP levels during acute gouty attack; the changes in SUA levels in these groups are shown in Figure 1. Both groups of patients, those with low CRP (Figure 1B: < 1.0 mg/dl) and those with high CRP (Figure 1C: > 1.0 mg/dl), exhibited significantly increased SUA after the acute attack. However, SUA during the attack in the high CRP group was significantly lower than that in the low CRP group (8.2 ± 1.1 vs 6.8 ± 1.4 mg/dl; $p < 0.005$, Mann-Whitney U test).

To determine the relationships between these variables, correlations between these variables and changes in SUA levels or indices of uric acid excretion were evaluated (Table 2). The percentage change in SUA level during the attack was significantly correlated with percentage change in FEua, and strongly correlated with CRP and IL-6 levels. However, the percentage change in FEua during the attack was significantly correlated with CRP and cortisol levels. The percentage change in ER was correlated with the percentage change in FEua and cortisol levels; however, the percentage change in ER was not correlated with that in SUA levels, CRP, or IL-6. CRP was correlated with IL-6 and cortisol levels, but IL-6 was not significantly correlated with cortisol level during the attack.

DISCUSSION

Our findings clearly demonstrate that SUA level decreased during acute gouty arthritis, consistent with an earlier report[5]. Since the percentage change in SUA was associated with that in FEua, the overexcretion of uric acid into urine is a possible means of lowering uric acid levels during acute gouty arthritis.

Gouty arthritis is a sudden event for patients and thus it is difficult to regulate all circumstantial factors in clinical research, including the timing of sample collection and dietary instructions. However, effects of diuretics, urate lowering agents, and alcoholic beverages were excluded from this study. NSAID were used for treatment of gouty arthritis, and the majority of patients received naproxen, which is known to be effective against gouty arthritis without changing SUA level[8]. Thus, it is clear that SUA levels during acute gouty arthritis are lower than those after attacks, as reported by Logan, *et al*[5]. During the acute phase, normal SUA level was found in 49% in our cases, consistent with the results of Logan, *et al* (43%).

Table 1. Variables of all patients during and after acute gouty attack. Values are mean ± SD (No. of patients).

	SUA, mg/dl	CRP, mg/dl	IL-6, pg/ml	Cortisol, pg/ml	ACTH, μg/dl	FEua, %	ER
During attack	7.54 ± 1.40 (41)	2.92 ± 4.43 (41)	2.73 ± 2.43 (21)	8.68 ± 2.43 (21)	26.9 ± 11.3 (21)	5.69 ± 1.90 (21)	0.43 ± 0.15 (21)
After attack	8.53 ± 0.94** (41)	0.41 ± 059** (41)	0.83 ± 1.12* (21)	8.49 ± 2.87 (21)	31.4 ± 17.2 (21)	5.17 ± 1.89 (21)	0.44 ± 0.18 (21)

**p < 0.0001; *p < 0.005. SUA: serum uric acid; CRP: C-reactive protein; IL-6: plasma interleukin 6, ACTH: plasma adrenocorticotropic hormone; FEua: fractional excretion of uric acid; ER: excretion rate.

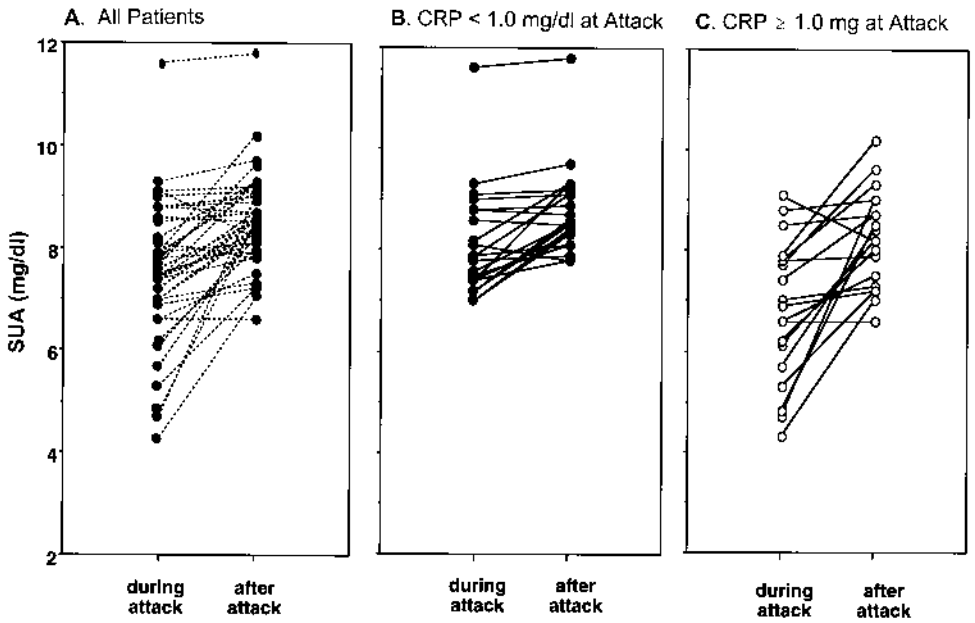

Figure 1. Changes in serum uric acid levels during and after acute gouty attack are shown. Patients were grouped by CRP level during the acute gouty attack. Groups with low CRP (B: < 1.0 mg/dl, n = 22) and high CRP (C: ≥ 1.0 mg/dl, n = 19) showed a significant increase in serum uric acid after the acute attack (B: $p < 0.0005$, C: $p < 0.001$, Wilcoxon signed-ranks test). However, serum uric acid during the attack in the high CRP group was significantly lower than that in the low CRP group ($p < 0.005$, Mann-Whitney U test).

It is intriguing that the change in SUA was closely associated with CRP and IL-6 levels and that change in FEua was significantly correlated with CRP level during acute arthritis. Moreover, our data showed that the change in SUA was associated with change in FEua but not with ER. FEua would be a marker for the renal tubular response of uric acid after glomerular filtration, while ER would be an indicator of glomerular filtration response of SUA[6,7]. These findings indicate the involvement of an acute inflammatory process in the excretion of uric acid into urine would be caused by a certain change in renal tubular response.

Recently, an exploratory clinical study reported decreased SUA levels when human recombinant IL-6 (hrIL-6) was administered to patients with refractory thrombocytopenia[9]. In that study, a reversible increase in urinary excretion of uric acid along with a reduction in SUA level was noted during infusion of recombinant IL-6. This observation indicates that IL-6 has an ability to reduce SUA level. Presumably, IL-6 could facilitate urinary excretion of uric acid, although this might not be a direct effect of IL-6.

IL-6 is a proinflammatory cytokine that is rapidly expressed upon stimulation[10], and is augmented in joint fluid and serum of patients with acute gouty arthritis[11-15]. Thus, it is reasonable to hypothesize that augmentation of IL-6 may induce excretion of uric acid into the urine during gouty arthritis. In our study, IL-6 levels during gouty attacks were not correlated with change in urinary excretion of uric acid, but were correlated with change in serum UA. That IL-6 levels in our study (2.73 ± 2.43 pg/ml) were much lower than those in the hrIL-6 injection study (22.7 pg/ml)[9] could explain this phenomenon.

According to our findings, however, CRP had a stronger

Table 2. Correlations between uric acid metabolism and inflammation.

	Percentage Change in SUA During Attack	CRP	IL-6	Cortisol	Percentage Change in ER During Attack
Percentage change in FEua during attack	0.447*	0.498*	0.418	0.534*	0.981***
Percentage change in ER during attack	0.281	0.398	0.332	0.543*	
Cortisol	0.331	0.460*	0.242		
IL-6	0.630**	0.645**			
CRP	0.762***				

*** $p < 0.0001$; ** $p < 0.005$; * $p < 0.05$.

relationship with the changes in both SUA and FEua; also, CRP had a positive correlation with IL-6 and cortisol.

IL-6 is an essential component of inflammation and has effects on the expression of other proinflammatory molecules[16,17].

Recently, cytokines including IL-6 have been shown to activate the hypothalamo-pituitary-adrenocortical axis[18,19]. Cortisol might be secreted by this pathway in gouty arthritis. Pain associated with arthritis causes cortisol release, and this has been implied to have a uricosuric effect[3]. Administration of ACTH for the treatment of gouty arthritis did not change SUA levels[20]; however, a continuous ACTH loading test in a patient with isolated ACTH deficiency showed that glucocorticoids have a direct effect on the renal clearance of uric acid[21]. In our study, we measured cortisol and ACTH levels on visits of patients to the hospital, but the time of day of testing may need to be considered given the possibility of circadian variation. However, cortisol levels were low even during gouty arthritis, yet were also correlated with 2 changed indices of uric acid excretion. Thus, cortisol might have participated in lowering of uric acid levels during acute gout.

IL-6 is secreted from renal tubular cells under certain conditions such as renal injury[22-25]. However, the effects of IL-6 on renal tubular cells have not been well documented. Recently, investigations of the urate transporter have been extensively performed[26], and gelactin-9 has been identified as a human urate transporter[27]. Since IL-6 is known to affect the transcription of multiple genes, accelerated gene expression of the urate transporter might play a role in the mechanism responsible for decreased SUA levels during acute gouty attacks. The effects of IL-6 and cortisol on the expression of gelactin-9 are not yet known, and *in vitro* studies on the expression of the urate transporter might clarify these potential mechanisms of lowering SUA level during acute gouty arthritis.

We demonstrated that the decrease in serum uric acid during acute gouty arthritis is associated with increased urinary excretion of uric acid; an inflammatory process may play a role in the mechanism of this phenomenon.

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