Is the Plasma Uridine Level a Marker of the Overproduction of Uric Acid?

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To determine whether the plasma level of uridine can be used to identify patients with gout, the plasma concentration of uridine was determined in patients with gout and normal subjects. Plasma uridine was significantly higher in patients with gout than in normal subjects. It was also significantly higher in patients with gout of the overexcretion (of uric acid) type than in those with gout of the underexcretion type. Plasma uridine was used to classify gout patients into underexcretion and overexcretion types, with a diagnostic accuracy of 92.5%. Results indicate that the plasma uridine concentration may be a marker of uric acid production and can be used to separate hyperuricemia into the overexcretion and underexcretion types.

HYPERURICEMIA leads to the deposition of urate crystals in the joints, subcutaneous tissue, and kidney and other organs. Patients with gout may suffer from arthritis (gouty arthritis) and nephritis (gouty kidney) induced by crystal deposition. However, since the availability of probenecid, a uricosuric agent,[1] and allopurinol, a xanthine oxidase inhibitor,[2,3] hyperuricemia has been easily controlled. Hyperuricemia is usually classified into the overexcretion type caused by renal overexcretion of uric acid, indicating overproduction of uric acid, and the underexcretion type caused by renal underexcretion of uric acid. Each type may be of primary or secondary origin. Classification is based on the 24-hour urinary excretion of uric acid and the renal clearance of uric acid. Treatment of hyperuricemia in Japan is commonly based on this classification. Allopurinol is usually administered to treat gout of the overexcretion type, and a uricosuric agent (probenecid, sulfinpyrazone, or benzbromarone[4]) to treat the underexcretion type. However, there is no clinical method for classifying the type of gout with ease and accuracy.

We recently demonstrated that the abrupt loss of adenosine triphosphate (ATP) increases the plasma concentration of uridine after ingestion of ethanol or infusion of fructose or xylitol,[5,6] suggesting that an increase in purine degradation may coexist with an increase in pyrimidine degradation in patients with primary gout of the overexcretion type. An increase in pyrimidine degradation accompanied by purine degradation may lead to a high plasma concentration of uridine (Fig 1). Based on this hypothesis, in the present study we measured the plasma concentration of uridine in normal subjects and in patients with gout, and investigated whether plasma uridine may reflect the production of uric acid in patients with gout. If so, we sought to determine whether it would differentiate overexcretion gout from underexcretion gout.

SUBJECTS AND METHODS

Subjects and Protocol

The subjects were 54 male gout patients with normal creatinine clearance and a mean age of 46.1 ± 10.5 years and 36 male control subjects aged 49.0 ± 10.1 years. All patients met criteria for primary gout as outlined by the American Rheumatism Association.[7] After informed consent was obtained, all medication was withheld starting 1 month before the study. Alcoholic beverages were withheld starting 1 week before the study. Based on replies to a questionnaire, purine intake was 150 to 250 mg/d. Control subjects were randomly selected from applicants for an annual medical check-up and exhibited normal results on urinalysis, complete blood cell counts, and routine biochemical analyses. After blood sampling, 24-hour urine output was collected from the patients with gout. In addition, 1-hour urine output was collected twice and blood was drawn at the midpoint of each of these 1-hour urine collections, following an overnight fast except for water. Uric acid concentrations were determined in plasma and urine, and 24-hour excretion and clearance of uric acid were calculated. Patients with gout were grouped according to the results of 24-hour urinary uric acid excretion in millimoles per square meter of body surface area, and uric acid clearance. Patients with excretion of urinary uric acid greater than 2.85 mmol/m^2 were classified as the overexcretion type, and those with urinary uric acid excretion of less than 2.84 mmol/m^2 and uric acid clearance of less than 6.0 mL/min were classified as the underexcretion type. In normal subjects, 24-hour urinary uric acid excretion was 2.26 ± 0.29 mmol/m^2 and uric acid clearance was 9.01 ± 1.45 mL/min. Hyperuricemia is attributed to overproduction or underexcretion of uric acid. A patient with gout not meeting the criteria just described was classified as the normal type and excluded from this study, with one exception included in the evaluation of correlations. This patient was aged 60 years and had a body mass index (BMI) of 21.8, plasma uric acid 564 μmol/L, plasma uridine 5.12 μmol/L, uric acid clearance 6.5 mL/min, and 24-hour urinary uric acid excretion 2.13 mmol/m^2. Although this patient had normal values for 24-hour urinary excretion and uric acid clearance, the uric acid clearance was near the lower limit of normal.

Blood and Urine Analyses

Blood samples were drawn into syringes after an overnight fast and placed into test tubes containing EDTA. The plasma was then immediately separated to prevent leakage of uridine and hypoxanthine from the blood cells. Plasma concentrations of uridine, hypoxanthine, and xanthine were determined by high-performance liquid chromatography as described previously.[8] Plasma concentrations of uric acid, creatinine, and triglyceride were determined with an autoanalyzer using specific enzymatic methods. Urinary concentrations of uric acid and creatinine were similarly determined.

Chemicals

All chemicals, including uridine and uric acid, were purchased from Wako Pure Chemical Industries (Osaka, Japan).

Statistics

Values are expressed as the mean ± SD. The significance of differences in means of the variables was analyzed by a two-tailed *t* test.

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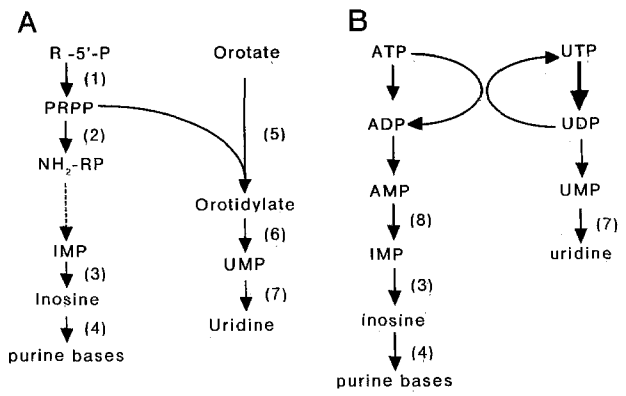

Fig 1. Relationship between uridine and purine metabolism. (A) Relationship between de novo purine synthesis and de novo pyrimidine synthesis and their degradation; (B) relationship between ATP consumption–induced purine degradation and pyrimidine degradation. R-5′-P, ribose-5′-phosphate; IMP, inosine monophosphate; UMP, uridine monophosphate; purine bases, hypoxanthine + xanthine + uric acid; 1, PRPP synthetase; 2, amidophosphoribosyltransferase; 3, purine 5′-nucleotidase; 4, purine nucleoside phosphorylase; 5, orotidylate pyrophosphorylase; 6, orotidylate decarboxylase; 7, pyrimidine 5′-nucleotidase; 8, AMP deaminase.

The relationship between variables was expressed by a correlation coefficient. P less than .05 was considered statistically significant.

RESULTS

Age, BMI, Plasma Uric Acid, and Plasma Triglyceride

As expected, the plasma uric acid level was higher in patients with gout than in control subjects. However, age, BMI, and plasma triglyceride level did not differ in patients with gout versus control subjects (Table 1).

Plasma Uridine

The plasma concentration of uridine was higher in patients with gout (6.04 ± 1.39 μmol/L) than in normal subjects (4.93 ± 1.13 μmol/L, $P < .001$), and was also higher in patients with gout of the overexcretion type (6.83 ± 0.80 μmol/L, $P < .001$) versus the underexcretion type (4.86 ± 0.96 μmol/L). However, the plasma concentration of uridine in patients with gout of the underexcretion type did not differ from that in control subjects (Fig 2).

Relationship of Plasma Uridine and Plasma Triglyceride to Other Parameters

Plasma uridine concentration was correlated with 24-hour urinary uric acid excretion per body surface area ($r = .60$, $P < .001$; Fig 3), but not with uric acid clearance. Plasma triglyceride concentration was not correlated with either 24-hour urinary uric acid excretion per body surface area of uric acid clearance (data not shown).

Table 1. Clinical Features of the Patients With Gout and Control Subjects

Group	Age (yr)	BMI (kg/m²)	Triglyceride (mmol/L)	Uric Acid (μmol/L)
Gout (n = 54)	46.1 ± 10.5	23.6 ± 2.4	2.06 ± 1.03	512 ± 56*
Control (n = 36)	49.0 ± 10.1	24.4 ± 2.9	1.78 ± 0.83	315 ± 48

*$P < .01$ *v* control.

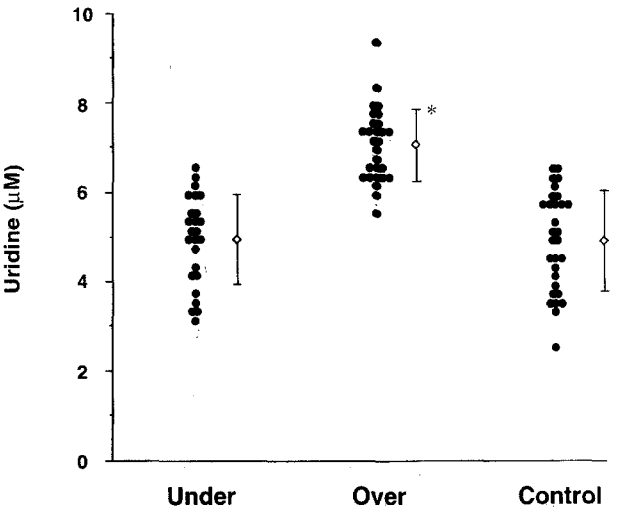

Fig 2. Plasma concentration of uridine in patients with gout of the underexcretion (under) and overexcretion (over) types and in control subjects. *$P < .001$ *v* underexcretion type.

Plasma Concentrations of Purine Bases and Triglyceride in Gout

Plasma concentrations of uric acid, hypoxanthine, and xanthine did not differ in patients with gout of the underexcretion type versus the overexcretion type (Table 2). In addition, plasma uridine was not correlated with plasma hypoxanthine, xanthine, uric acid, or triglyceride in patients with gout (data not shown).

Classification of Hyperuricemia by Plasma Uridine Level

When the cutoff level of 6.2 μmol/L plasma uridine was used to separate patients with gout into two groups (underexcretion type and overexcretion type), diagnostic accuracy was 92.5% ($P < .01$; Table 3).

DISCUSSION

Although hyperuricemia in patients with gout is caused by several factors, it is classified clinically as being due to overexcretion (overproduction) or underexcretion. Overexcretion hyperuricemia that is caused by purine degradation is classified as due to either enhanced de novo purine synthesis or excessive ATP consumption. Enhanced de novo purine synthesis causes an acceleration of purine degradation, resulting in an increased production of uric acid. Typical cases involve phosphoribosyl pyrophosphate (PRPP) synthetase overactivity and hypoxanthine guanine phosphoribosyl transferase (HGPRT) deficiency. Since de novo purine synthesis uses PRPP, PRPP synthesis must be enhanced along with increased de novo synthesis. An enhanced PRPP synthesis may increase de novo pyrimidine synthesis. The resultant enhancement of de novo pyrimidine synthesis may accelerate pyrimidine degradation, leading to increased production of uridine (Fig 1). We detected a high plasma concentration of uridine in a patient with a deficiency of HGPRT, a typical case of an enhanced de novo

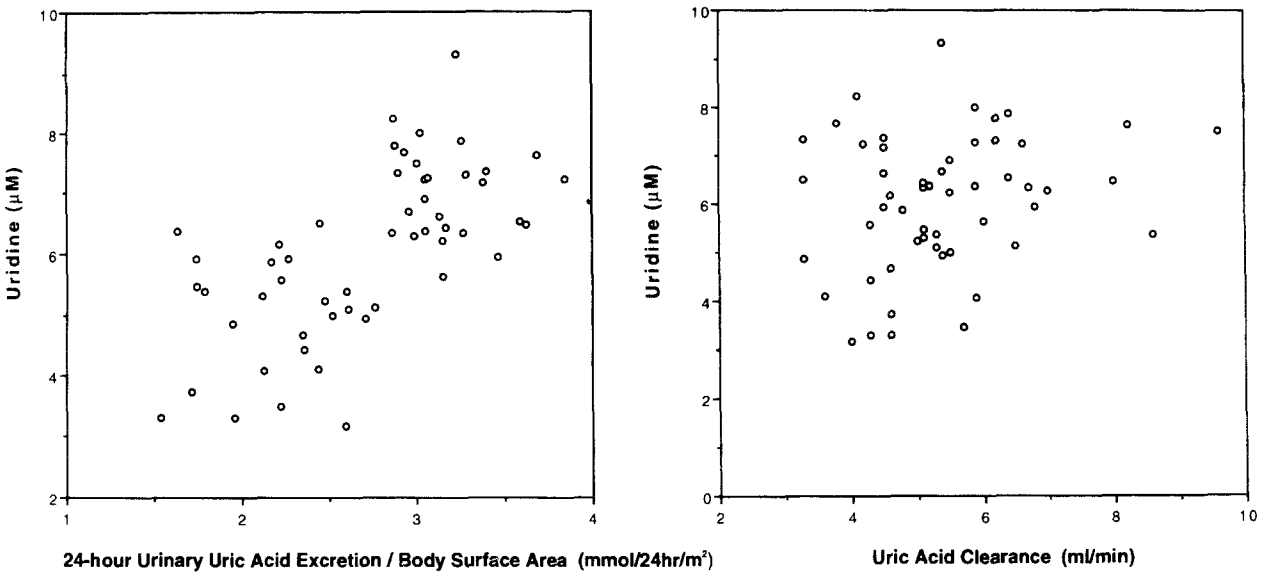

Fig 3. Relationship of plasma uridine concentration to 24-hour urinary uric acid excretion per body surface area and to uric acid clearance. The correlation between plasma uridine concentration and 24-hour urinary uric acid excretion was statistically significant ($r = .6$, $P < .001$), but the correlation between plasma uridine concentration and uric acid clearance was not.

purine synthesis (T. Yamamoto, unpublished data, August 1996).

The excessive consumption of ATP also accelerates purine degradation, resulting in an increased production of uric acid. Both adenosine monophosphate (AMP) deaminase overactivity[9] and aldolase B deficiency,[10] which enhance ATP consumption, have been described in patients with gout. Previous studies[11,12] demonstrated that abrupt consumption of ATP increased purine and pyrimidine degradation, resulting in overproduction of hypoxanthine and uridine (Fig 1). In fact, plasma concentrations of purine bases and uridine are increased by ethanol, fructose, and xylitol,[5,6] which are known to consume ATP in their metabolism. In the present study, the plasma concentration of uridine was higher in patients with gout of the overexcretion type versus the underexcretion type (Fig 2). In addition, the plasma concentration of uridine in patients with gout was correlated with 24-hour urinary excretion of uric acid (Fig 3). These results suggest that plasma uridine may be a marker for the production of uric acid, irrespective of whether purine degradation is induced by enhanced de novo purine synthesis or by ATP consumption. Although patients with gout have hyperuricemia, a high plasma uric acid level does not necessarily indicate uric acid production, since plasma uric acid is regulated by both uric acid production and uric acid excretion. When excretion of uric acid in the urine decreases, the plasma uric acid level is markedly elevated regardless of whether uric acid production has been increased. The concentration of oxypurines in plasma may be a sensitive marker of purine degradation. Acceleration of purine degradation in tissue that lacks xanthine dehydrogenase is reflected in an increase in the plasma concentration of hypoxanthine,[3,14] since hypoxanthine leaks into the blood as an end product of purine degradation. Accordingly, in patients with glycogen storage disease type VII, V, or III, plasma hypoxanthine can be a sensitive marker of purine degradation in muscle, as described previously.[14-16] In contrast, oxypurines are oxidized to uric acid by xanthine dehydrogenase in the liver and intestine. Xanthine dehydrogenase may be sufficient to immediately oxidize the oxypurines produced by accelerated purine degradation in the liver, since the increase in the plasma concentration of oxypurines is small in patients with a deficiency of HGPRT,[17] as compared with that of uric acid. In addition, renal excretion of hypoxanthine and xanthine is decreased in patients with gout of the underexcretion type.[17] Therefore, the plasma oxypurine level does not simply reflect purine degradation in patients with gout, as suggested by Table 2. The serum triglyceride level is positively correlated with 24-hour urinary uric acid excretion.[18] However, in the present study, plasma triglyceride level was not correlated with 24-hour urinary excretion or with plasma uridine concentration in patients with gout, suggesting that in such patients plasma triglyceride level is not a marker of uric acid production.

Uridine is a product of pyrimidine degradation and reflects pyrimidine degradation in the body. It also reflects accelerated purine degradation after infusion of fructose or xylitol or

Table 2. Plasma Concentrations of Purine Bases in Patients With Gout of the Overexcretion or Underexcretion Type

Group	Hypoxanthine (μmol/L)	Xanthine (μmol/L)	Uric Acid (μmol/L)
Underexcretion (n = 25)	0.26 ± 0.07	0.12 ± 0.01	511 ± 58
Overexcretion (n = 28)	0.28 ± 0.08	0.11 ± 0.02	512 ± 55

Table 3. Classification of Gout Patients by Plasma Uridine Level

Type	Plasma Uridine <6.2 μmol/L	Plasma Uridine >6.2 μmol/L
Overexcretion (n = 28)	2	26
Underexcretion (n = 25)	23	2

NOTE. Diagnostic accuracy is 92.5% ($P < .01$, χ^2 test).

ingestion of ethanol.[5,6] The present study demonstrated that plasma uridine was high in patients with gout of the overexcretion type and served to separate patients with gout into two groups (overexcretion type and underexcretion type). Our results suggest strongly that the plasma uridine concentration can be a marker of uric acid production in the body, and that it can easily be used to divide patients with gout into the underexcretion and overexcretion types.

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