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Original article

Patients with gout differ from healthy subjects in renal response to changes in serum uric acid

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ABSTRACT

Objective: Our objectives were to determine whether a change in serum uric acid (sUA) resulted in a corresponding change in the fractional excretion of uric acid (FEUA) and whether the renal response was different in patients with gout versus healthy subjects.
Methods: FEUA was calculated from previously published studies and four new phase I studies in healthy subjects and/or patients with gout before and after treatment to lower or raise sUA. Treatments included xanthine oxidase inhibitors to lower sUA as well as infusion of uric acid and provision of a high-purine diet to raise sUA. Plots were created of FEUA versus sUA before and after treatment. For the phase I studies, percent change in FEUA per mg/dL change in sUA was calculated separately for healthy subjects and patients with gout, and compared using Student's *t* test.
Results: Analysis of previously published data and the new phase I clinical data indicates that changing sUA by a non-renal mechanism leads to a change in FEUA. The magnitude of change is greater in subjects with higher baseline FEUA versus patients with gout. Healthy subjects excrete more urate than do patients with gout at physiological urate-filtered load; this difference disappears when the urate-filtered load is decreased to ~5000 mg/24 hours.
Conclusion: These observations are consistent with a less saturated urate reabsorption system in patients with gout versus healthy subjects, resulting in elevated retention of uric acid. Further investigation could lead to the discovery of mechanisms responsible for the etiology of hyperuricemia/gout.

1. Introduction

The amount of uric acid in the body is dependent upon endogenous synthesis and dietary intake of purines and excretion, and the concentration of uric acid in blood is determined by the balance between uric acid production and excretion. Endogenous synthesis accounts for approximately two thirds and dietary intake for one third of purine production [1,2]. Most of the uric acid is excreted by the kidney (70%), with the rest (30%) eliminated in the gut [1,3]. At the level of the glomeruli, uric acid is freely filtered from the blood. In healthy people, roughly 90% of the filtered urate is reabsorbed in the proximal convoluted tubules and about 10% is excreted in the urine [1,2].

Gout is caused by hyperuricemia, which is defined as serum uric acid (sUA) levels of > 6.8 mg/dL [4,5]. Sustained hyperuricemia can lead to deposition of monosodium urate crystals in musculoskeletal structures and other tissues and cause chronic inflammation, acute gout flares, and potentially chronic arthritis with joint damage and disfiguring tophi [4,5]. Hyperuricemia is caused primarily (in 80%–90% of subjects) by inefficient renal uric acid excretion, with diet and overproduction of uric acid playing a major role in approximately 10%–20% of subjects [6]. It is possible for individuals to have both components of overproduction and inefficient renal excretion of uric acid mediating their disease [7].

Fractional excretion of uric acid (FEUA) is defined as the percentage of uric acid filtered by the kidney that is excreted in the urine. It is well documented that FEUA affects sUA levels, where the higher the FEUA, the lower the sUA in people without an impairment in renal function. Most previous studies have reported changes in the renal handling of uric acid when sUA levels were altered, but not all reported or calculated FEUA [8–11]. As part of our report, additional analysis of the results from these older studies was performed to calculate FEUA. In addition, we report and contrast the renal response to alterations in sUA levels in healthy subjects and patients with gout given a xanthine oxidase inhibitor (XOI)

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during phase I clinical studies. The objectives of this work were to determine:

- whether a change in sUA results in a corresponding change in FEUA, and;
- whether the renal response was different in patients with gout compared with healthy subjects.

2. Methods

2.1. Additional analysis of previous studies

In four previously published studies that reported changes in the renal handling of uric acid when sUA levels were altered, one reported FEUA and one reported only urate clearance, while the other two reported enough data to calculate FEUA. FEUA is calculated as the clearance of uric acid divided by the clearance of inulin or creatinine. Berliner et al. [8] infused uric acid into healthy subjects to raise plasma uric acid levels and reported the rate of urate excreted and the rate of urate filtered. FEUA was calculated by dividing the urate excreted by the urate filtered. Khosravan et al. [9] lowered sUA levels in healthy subjects by administering increasing doses of febuxostat, an XOI, for 14 days and reported uric acid clearance without inulin or creatinine clearance. Assuming there was no change in glomerular filtration rate during the study, the change in uric acid clearance should parallel that in FEUA. Nugent and Tyler [10] raised sUA levels in healthy subjects by giving them a high-purine diet or ribonucleic acid (RNA) capsules, while patients with gout were studied without any dietary changes. No calculation was required as the results were reported as the ratio of the clearance of uric acid (CU) to that of inulin (CIN), which is FEUA. Puig et al. [11] raised sUA levels in healthy subjects by giving them oral RNA and also lowered sUA levels in both healthy subjects and patients with gout by administering the XOI, allopurinol. They reported the amount of urinary uric acid, sUA levels, and creatinine clearance. In order to calculate FEUA, uric acid clearance was first calculated by dividing urinary uric acid by the sUA concentration (plus unit adjustment); uric acid clearance was then divided by creatinine clearance to yield FEUA.

2.2. Analysis of phase I studies

Participants who had completed any one of four phase I/Ib studies and had sUA and FEUA values measured at baseline and day 7 were included in the analysis. None of the participants were taking diuretics. All participants received an XOI once daily for 7 days. Healthy subjects received febuxostat 40 or 80 mg while patients with gout received febuxostat 40 or 80 mg, or allopurinol 300 mg. Healthy subjects were aged ≥ 18 and ≤ 45 years, had a body mass index of ≥ 18 and $\leq 30\,kg/m^2$, and sUA ≥ 5 mg/dL. Patients with gout were aged 18–80 years, inclusive, with a diagnosis of gout, and sUA ≥ 8 mg/dL. The diagnosis of gout was based on American Rheumatism Association Criteria for the Classification of Acute Arthritis of Primary Gout [12].

Blood and urine samples were collected at specific times over a 24-hour period for the measurement of sUA, and serum creatinine and urine concentrations of uric acid and creatinine. Uric acid and creatinine were determined by standard enzymatic methods. This 24-hour sampling was performed on both day−1 (baseline) and day 7. FEUA was calculated as urate clearance (CLUR) divided by creatinine clearance (CLCr) × 100, based on 0–24-hour urine collection. Plots were created of change in FEUA versus baseline FEUA, as well as FEUA versus sUA and urinary uric acid excretion (UUE) versus urate-filtered load. UUE is the amount (mg) of uric acid excreted in the urine in 24 hours. The urate-filtered load (mg/min) is calculated by glomerular filtration rate (mL/min, estimated by CLCr) × sUA (mg/mL). Change in FEUA per mg/dL change in sUA was calculated separately for healthy subjects and patients with gout, and the results compared using Student's *t* test.

3. Results

3.1. Analysis of published studies

We analyzed FEUA or uric acid clearance from four previously published studies and then compared FEUA or uric acid clearance versus sUA or plasma uric acid (pUA) levels in each study (Fig. 1). As expected, gout patients in these studies had lower baseline FEUA overall compared with healthy subjects. In all of the studies, the results showed that there is a direct relationship between change in sUA (or pUA) and change in FEUA. When sUA is increased by feeding purines or injection of uric acid, FEUA increases. Conversely, when the sUA is lowered, FEUA is lowered. This is true for all of the subjects/groups except for 1 of the 11 groups in the Khosravan paper [9], where the lowered sUA by 160 mg febuxostat was accompanied by an increase in uric acid clearance (Fig. 1D). Though the data are limited for comparing gout patients versus healthy subjects, there appears to be a difference in the slope of the response (Fig. 1C) [11]. This suggestion of a difference between gout patients and healthy subjects was further investigated using data from four phase I studies.

3.2. Analysis of phase I studies

A total of 56 subjects were included in the analysis (healthy subjects, $n = 21$; patients with gout, $n = 35$). Patients with gout were older, weighed more, and had higher sUA levels than healthy subjects (Table 1). Baseline FEUA was significantly greater in healthy subjects than patients with gout ($P < 0.0001$; Fig. 2). Both groups had normal renal function, with mean (range) CLCr of 116 (86–158) mL/min in healthy subjects and 136 (80–192) mL/min in patients with gout.

Mean baseline sUA levels ranged from ~6–7 mg/dL for healthy subjects in the febuxostat 40 or 80 mg treatment groups and from ~9–10 mg/dL for patients with gout in the allopurinol 300 mg or febuxostat 40 or 80 mg treatment groups (Fig. 3). Mean baseline FEUA ranged from ~6%–7% in healthy subjects and was ~4% in patients with gout. The average change in sUA on day 7 ranged from −2.5 to −4.7 mg/dL across the groups, while the change in FEUA ranged from −1.4% to −3.2% for healthy subjects and from −0.1% to −0.9% for patients with gout. When the change in FEUA was plotted against baseline FEUA for all subjects, the correlation coefficient was −0.83 ($P < 0.0001$), indicating that the higher the baseline FEUA, the greater the reduction in FEUA (Fig. 4A). Thus, the baseline FEUA is correlated with FEUA response to sUA

Table 1
Demographic and baseline characteristics of study subjects.

	Healthy subjects	Patients with gout
n	21	35
Age, years, mean (range)	40.0 (22–61)	48.9 (21–74)
Male, *n* (%)	21 (100)	35 (100)
Ethnic origin, n (%)		
Asian	1 (4.8)	1 (2.9)
Black	6 (28.6)	8 (22.9)
White	13 (61.9)	25 (71.4)
Mixed	1 (4.8)	1 (2.9)
Body weight, kg, mean (SD)	82.0 (11.3)	102.9 (20.6)
Body mass index, kg/m^2, mean (SD)	26.4 (3.8)	32.6 (5.1)
Serum uric acid, mg/dL, mean (SD)	6.0 (1.0)	9.3 (1.2)
CLCr, mL/min, mean (range)	116 (86–158)	136 (80–192)

CLCr: creatinine clearance.