JCI The Journal of Clinical Investigation

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John H. Ayvazian, L. Fred Ayvazian

J Clin Invest. 1963;42(11):1835-1839. https://doi.org/10.1172/JCI104867.

Research Article

Journal of Clinical Investigation
Vol. 42, No. 11, 1963

CHANGES IN SERUM AND URINARY URIC ACID WITH THE DEVELOPMENT OF SYMPTOMATIC GOUT *

By JOHN H. AYVAZIAN AND L. FRED AYVAZIAN

(From the Medical Service, Veterans Administration Hospital, New York, N. Y.)

(Submitted for publication May 7, 1963; accepted August 1, 1963)

In a recent study of gouty subjects, urinary excretion of uric acid was noted to be greater in the symptomatic than in the asymptomatic subjects (1). Since, however, the groups of patients were small and the data unpaired, these observations were not analyzed further. A review of published reports revealed lack of agreement about changes in serum and urinary uric acid during clinically active gout. Brøchner-Mortensen (2), summarizing publications to 1939, called attention to German reports that uric acid excretion increased greatly during acute attacks of gout and subsided thereafter. Brøchner-Mortensen considered, however, that the reported fluctuations in uric acid excretion were inconstant when set against variations in medication and diet. Despite individual case reports indicating increased uricosuria during gouty attacks (3, 4), Stetten's view that "when an acute attack does occur no consistent changes in the quantity of uric acid in blood or urine are observed" (5), represents the consensus of current opinion.

The present study was designed to extend our previous findings by obtaining paired data from gouty men during symptomatic and asymptomatic phases of their disease, simultaneously eliminating, whenever possible, other factors that might influence uric acid metabolism and turnover.

METHODS

Over a 2-year span, data were collected from eleven subjects judged suitable for this study. All were men with previously established diagnoses of primary gout, with no detectable nephropathy, and with totally asymptomatic intercritical intervals. Pertinent data for all subjects are listed in Table I. Only three were later eliminated, two for failure to collect total urine output, and one because of the inadvertent medication with a uricosuric drug during a symptomatic episode. Ten of the subjects were followed over a single hospital admission; eight were admitted with acute arthritis and were studied before and after therapy with colchicine and relief of symptoms. The remaining two, RC and FC, were admitted for unrelated reasons and developed acute arthritis during the study. The eleventh subject, LM, was seen over two separate admissions, once for acute arthritis, when only acute-phase data were studied, and again, 2 years later, during ambulatory convalescence from myocardial infarction.

None of the subjects were on uricosuric drugs before the study. They were all fed a standard low-purine diet from at least 2 days before the start of the study. The daily diet contained 96 g protein, 85 g fat, and 257 g carbohydrate; the purine content was limited to 60 mg contained in one meat course given each day. Dietary intake was supervised daily. Three normal persons fed this diet for 7 to 11 days each stabilized their urinary excretion of uric acid within 24 to 48 hours, and thereafter their daily uric acid excretion did not vary by more than 68 mg from their individual mean 24-hour uric acid excretion. The subjects' total urine output was collected in 24-hour samples starting and ending at 8:30 a.m. Blood was drawn each day at the same hour. Collection and preservation of urine has been described (6). Uric acid was measured by the spectrophotometric method of Praetorius and Poulsen (7) with uricase, and creatinines were determined by Phillips' modification of the alkaline picrate method (8). Urinary 17-hydroxycorticosteroids were analyzed by the method of Silber and Porter (9).

Therapy during the acute phase of the study was limited to nonuricosuric analgesics. The acute phase of the study was terminated by iv colchicine therapy in order to avoid any possible gastroenteritis that might interfere with urine collection. The usual regimen was 3 mg intravenously, followed in 12 hours by maintenance oral medication. Six of the eight subjects admitted with acute arthritis responded within 24 to 48 hours. The remaining two required a second iv dose and were free of symptoms within 72 hours. Data obtained during this transitional phase are not included in this study, and showed only decreases in uric acid excretion to levels observed in the asymptomatic period. The asymptomatic phase of the study was marked from the time at which the patient became afebrile, ambulatory, and free of objective signs of arthritis or inflammation.

RESULTS

Clinical laboratory data from the eleven gouty subjects are listed in Table I. All had absolute

* Work supported by U. S. Public Health Service research grant AI 02757-05 from the National Institute of Allergy and Infectious Diseases, Bethesda, Md.

TABLE I

Summary of clinical data for gouty subjects

Subject	Age	Duration of gout	Blood urea nitrogen	Clearance endogenous creatinine	Leukocytes		Excretion of 17-hydroxycorticosteroid*	
					Asymptomatic	Symptomatic	Asymptomatic	Symptomatic
	years	*years*	*mg/100 ml*	*ml/min*	*cells/mm³*		*mg/24 hours*	
I.S.	41	8	20	131	9,380	10,100	9.4	11.8
M.V.	61	11	20	90	8,460	14,600		
D.F.	50	4	11	99	8,100	12,600		
P.G.	41	5	16	128	5,600	9,780		
R.C.	59	3	18	102	5,240	11,700	10.8	17.2
J.C.	58	3	17	98	7,770	19,000		
O.H.	44	7	17	105	7,800	19,500		
L.M.	40	6	16	124	7,200	13,400		
E.D.	53	4	13	97	7,160	18,800	9.3	12.6
A.R.	48	8	17	143	7,480	15,600	9.1	11.9
F.C.	44	2	14	110	9,420	15,800	16.2	31.3

* Normal range: 3.0 to 10.3 mg per 24 hours.

or relative leukocytosis during the symptomatic period. Also, all five subjects so studied had increased 24-hour urinary 17-hydroxycorticosteroid excretion during the arthritic state.

Eight of the eleven subjects were observed for 3 days before treatment with colchicine while they were symptomatic and for 3 more days while asymptomatic. For the remaining three subjects (DF, PG, and JC), data were collected for only 2 days for each period, since they received colchicine after the second day of the acute-phase study. The data are summarized in Table II, in terms of the mean values of serum and urinary uric acid and the renal clearance of uric acid for

TABLE II

*Summary of data on uric acid in symptomatic and asymptomatic periods of gout**

Subject	Asymptomatic period			Symptomatic period			Difference between periods		
	Serum	Urine	C_{ua}	Serum	Urine	C_{ua}	Serum	Urine	C_{ua}
	mg/100 ml	*mg/24 hours*	*ml/min*	*mg/100 ml*	*mg/24 hours*	*ml/min*	*mg/100 ml*	*mg/24 hours*	*ml/min*
I.S.	8.5 8.0–8.8	568 529–600	4.6 4.5–4.7	9.5 8.9–10.0	674 627–723	4.9 4.9–5.0	+1.0	+106	+0.3
M.V.	10.5 10.1–10.8	407 376–446	2.7 2.6–3.1	11.8 11.4–12.2	574 536–630	3.4 3.3–3.6	+1.3	+167	+0.7
D.F.	7.7 7.5–7.8	378 367–388	3.5 3.3–3.6	7.9 7.6–8.1	592 479–704	5.2 4.4–6.0	+0.2	+214	+1.7
P.G.	8.1 7.9–8.3	566 544–588	4.9 4.6–5.2	8.4 7.6–8.9	793 722–863	6.7 6.6–6.7	+0.3	+227	+1.8
R.C.	6.1 5.9–6.2	556 509–595	6.4 5.8–6.7	6.1 6.0–6.2	797 713–872	9.0 8.0–9.8	0	+241	+2.6
J.C.	6.6 6.4–6.8	350 325–374	3.7 3.5–3.8	7.0 6.9–7.1	606 597–615	6.0 6.0	+0.4	+256	+2.3
O.H.	6.6 6.5–6.8	421 377–495	4.4 3.9–5.2	6.8 6.0–7.4	706 701–717	7.2 6.7–8.1	+0.2	+285	+2.8
L.M.	10.5 10.3–10.6	784 770–802	5.2 5.0–5.4	9.7 9.1–10.1	968 934–1,025	6.9 6.4–7.2	−0.8	+184	+1.7
E.D.	8.2 7.7–8.6	451 432–475	3.8 3.8–3.9	8.9 7.8–9.9	792 689–918	6.3 4.8–8.2	+0.7	+341	+2.5
A.R.	6.8 6.6–7.0	602 562–626	6.2 5.6–6.6	7.1 6.8–7.3	927 837–1,091	9.1 8.2–10.4	+0.3	+325	+2.9
F.C.	11.3 10.9–11.5	522 505–533	3.2 3.1–3.4	7.9 7.6–8.2	1,060 900–1,142	9.4 8.0–10.4	−3.4	+538	+6.2

* Mean values and ranges are given. C_{ua} = renal clearance of uric acid.

TABLE III

Uric acid data in two subjects developing arthritis

Day	Subject RC			Subject FC		
	Serum	Urine	Clinical state	Serum	Urine	Clinical state
	mg/100 ml	*mg/24 hours*		*mg/100 ml*	*mg/24 hours*	
1	6.1	509	Asymptomatic	10.9	527	Asymptomatic
2	6.2	595	Asymptomatic	11.4	505	Asymptomatic
3	5.9	566	Asymptomatic	11.5	533	Asymptomatic
4	6.3	590	Asymptomatic	11.7	495	Asymptomatic
5	6.3	603	Asymptomatic	12.0	603	Rhinitis and pharyngitis
6	6.2	715	Asymptomatic	11.3	571	Rhinitis and pharyngitis
7	6.0	806	Arthritis	12.1	671	Sinusitis
8	6.2	872	Arthritis	10.7	779	Sinusitis
9	6.2	713	Arthritis	8.2	1,142	Arthritis
10				7.6	1,137	Arthritis
11				7.8	900	Arthritis

each period and their ranges. Greater excretions and renal clearances of uric acid were found in all eleven subjects while their disease was symptomatic; excretion increased from 106 to 538 mg of uric acid per 24 hours, and the calculated renal clearance rose by 0.3 to 6.2 ml per minute. Serum levels of uric acid changed variably, rising in eight subjects, falling in two, and remaining virtually unchanged in one. Statistical analysis by means of the Wilcoxan's signed-ranks test for matched pairs (10) shows the increased urinary excretion and renal clearance of uric acid to be significant with a p of less than 0.01, whereas the changes in the serum values are not statistically significant.

Data from the two subjects who developed acute arthritis during the study are listed in detail in Table III. Both subjects increased their excretion of uric acid before developing clinical arthritis. FC developed a viral infection of the upper respiratory tract 4 days before and an acute, purulent sinusitis 2 days before his arthritis became symptomatic. No obvious precipitating cause was detected for RC, but his uric acid excretion increased at least 24 hours before the development of an acute monoarthritis, which was noted at the completion of the seventh day of urine collection.

The failure to observe any significant changes in the serum uric acid of the gouty subjects during the two clinical phases prompted an additional study. Similar studies were conducted on a group of nongouty persons with inflammation and obviously increased nucleic acid production. Table IV lists the data obtained from seven subjects with acute nongouty arthritis or suppurative lung disease. In all seven, uric acid excretion and clearance were considerably elevated, despite the absence of hyperuricemia. Serum uric acid levels ranged from 2.2 to 4.7 mg per 100 ml, well within the normal range, whereas urinary excretion and clearance ranged from 733 to 1,330 mg per 24 hours and 15.6 to 29.0 ml per minute, values two to three times the normal.

DISCUSSION

Our observations raise two questions. First, what is the source or mechanism of the increased uric acid excretion and clearance in symptomatic gout? Second, are these changes the cause or the result of the arthritis? If a significant change in serum uric acid had accompanied the increased uric acid excretion, then these changes could have been attributed to either increased production of uric acid, or increased renal tubular clearance, depending on the direction of change in serum levels.

TABLE IV

Uric acid data in seven nongouty subjects with active inflammation, or suppuration, or both

Subject	Diagnosis	Serum	Urine	C_{ua}*
		mg/100 ml	*mg/24 hours*	*ml/min*
SD	Pulmonary abscess	3.3	733	15.6
OW	Lobar pneumonia	4.3	1,330	21.5
MS	Bronchiectasis	4.5	1,280	19.8
OF	Septic arthritis	3.8	1,164	21.3
JP	Rheumatoid arthritis	2.2	918	29.0
CK	Rheumatoid arthritis	4.7	1,296	19.1
JI	Rheumatic fever	4.2	1,035	17.1

* Renal clearance of uric acid.

Certain observations, reported both here and previously, favor increased production of uric acid as the mechanism for the increased excretion. The leukocytosis observed during the symptomatic state (Table I) indicates increased nucleic acid production and, after degeneration of the leukocytes in the inflammatory area, increased uric acid production. A previously reported observation on the ability of iv administered desoxyribonuclease to increase uric acid excretion in symptomatic gouty subjects tends to confirm this concept (1). This enzyme, a DNA depolymerase, is capable of diffusing into inflammatory areas and depolymerizing DNA derived from susceptible leukocytes (11–13).

The failure to demonstrate an increase in serum uric acid levels argues against the concept of increased production. Recent studies have shown that increased uric acid load, in addition to producing increased renal clearance of uric acid, also increases serum levels (14–16). The observation, however, of normal serum uric acid levels in nongouty subjects with increased uric acid production secondary to suppurative and inflammatory diseases (Table IV) suggests that inflammation may modify the host response to an increased uric acid load. The increased urinary excretion of 17-hydroxycorticosteroids during the symptomatic state by five of the gouty subjects (Table I) implies an increased secretion of adrenal steroids during the pain and stress of the arthritis that would produce renal uricosuria (17) and possibly decrease serum levels despite an increased load.

The second question, whether the increased excretion of uric acid is a cause or effect of the arthritis, must also be answered speculatively. The increased uric acid excretion by two subjects before development of clinical arthritis (Table III) indicates the increase may be causally related. The classical observations that leukocytosis-stimulating episodes such as infection, surgery, or trauma are precipitating causes of arthritis (18–20) support this possibility. The arthritis itself, however, will stimulate further leukocytic response, and further nucleic acid and uric acid production, and, as Seegmiller, Laster, and Howell postulate, the inflammatory reaction becomes self-sustaining and self-enhancing (21).

SUMMARY

Data demonstrate that gouty subjects have a greater excretion and clearance of uric acid while they are symptomatic, but that their serum levels do not change predictably with the symptoms. The cause of these changes is unknown, but the leukocytosis and increased 17-hydroxycorticosteroid excretion observed during the arthritic state suggest the combined involvement of increased production of uric acid and steroid-induced renal uricosuria.

ACKNOWLEDGMENT

We are indebted for the excellent technical assistance of Miss Giannina Zatti and for the co-operation of Mr. Milton Weissman with the 17-hydroxycorticosteroid analyses.

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