

# The Effect of Control and Self-Medication of Chronic Gout in a Developing Country. Outcome After 10 Years

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## **ABSTRACT.**

**Objective.** We describe a 10 year observation of the effect of control of hyperuricemia compared with self-medication alone in patients with chronic gout.

**Methods.** We studied 299 consecutively self-referred Malayo-Polynesian men with chronic gout, mean age  $35 \pm 14.3$  SD years. Subjects comprised 228 cases with chronic gout without tophi or urolithiasis (Group 1) and 71 with those complications (Group 2). Attacks of acute gouty arthritis were treated with nonsteroidal antiinflammatory drugs (NSAID) and/or corticosteroids. After acute arthritis had settled, urate-lowering drugs were instituted in both groups combined with low dose colchicine and/or low dose NSAID for at least 0.5–2 years. Urate levels were maintained longterm at a mean of  $< 5$  mg/dl. After 10 years, the dropouts were traced and evaluated for comparison with baseline and those who remained in the study. In Group 2 the urate-lowering drugs were continued.

**Results.** Control of gout and hyperuricemia was achieved in all patients who remained under control: 91.6% of the 299 patients for at least 2 years (short-term), up to 5 years in 87.5% (medium term), and up to 10 years in 79.6% (longterm). In Group 1 (chronic gout without complication) only 36.8% had no attacks during 8 years, after they had tapered urate-lowering drug after the first 2 years of the study. In the 61 dropouts the intermittent symptomatic treatment and/or self-medication without longterm control of hyperuricemia resulted after 1 decade in chronic gout with more complications and associated conditions leading to increased morbidity, disability, and comorbidity, and 3 early mortalities.

**Conclusion.** By controlling hyperuricemia, improvement of the prognosis of chronic gout, comorbidity, and early death was achieved compared with self-medication alone. Self-medication in a developing country if continued unchecked may become a public health problem in a population with a high prevalence rate of gout. (J Rheumatol 2003;30:2437-43)

## *Key Indexing Terms:*

CHRONIC GOUT  
HYPERURICEMIA  
TREATMENT-FREE CONTROL  
SELF-MEDICATION

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The prevalence rates of gout in adult Malayo-Polynesian men in North Central Java are rural 1.7%<sup>1</sup> and urban 4.8%<sup>2</sup>; New Zealand Polynesian men (Maoris) show rates of 13.9% and New Zealand Caucasian men 5.8%<sup>3</sup>. These differences were associated with environmental risk factors. Increasing affluence and western lifestyle have increased the prevalence of gout and hyperuricemia in genetically predisposed Malayo-Polynesians and Polynesians<sup>1-3</sup>. In the USA the prevalence of self-reported gout in men was 3.1%<sup>4</sup>.

We describe a 10 year observation of the effect of control of hyperuricemia compared with self-medication alone in chronic gout.

## **MATERIALS AND METHODS**

A total of 307 consecutive self-referred Malayo-Polynesian men 30–45 years of age with chronic gout, first seen between January 1984 and January 1989, were observed for 10 years. A total of 228 men with chronic gout without (Group 1) and 71 with complications (Group 2) agreed to enter the study. Excluded were women with gout, men with gout combined with an autoimmune disease, and those with radiological chondrocalcinosis.

Gout was diagnosed when negative birefringent intracellular crystals of monosodium urate in the synovial fluid from an acutely inflamed joint were identified<sup>5</sup>. If no crystals were found or no synovial fluid could be aspirated, the diagnosis was carefully established by classification criteria for gout<sup>6</sup>. Radiographs were taken to exclude chondrocalcinosis. Tophi or ulcerating tophi were confirmed when urate crystals were found in the aspirate.

Chronic gout was defined when a patient had at least 3 attacks of acute arthritis per year, or when a tophus was confirmed.

Complications were defined when chronic gout was accompanied by tophi and/or history of urolithiasis. Associated conditions were: impaired renal function, hypertension,

hyperlipidemia, hyperglycemia, liver impairment, atherosclerosis, stroke, and myocardial infarction, which appeared after onset of chronic gout.

Control of gout was defined when a patient did not have an acute attack for at least 2 years with serum uric acid concentration maintained at  $< 5$  mg/dl.

Dropout was defined when a patient did not appear for scheduled laboratory monitoring and followup or stopped taking urate-lowering drugs.

Baseline laboratory tests included: serum urate, urea, creatinine, glucose, fasting lipids, urinalysis for hematuria and proteinuria, albumin and total protein, alkaline phosphatase, ALAT, ASAT, bilirubin, bilirubin–urine, gammaglutamyl transferase, lactate dehydrogenase, hemoglobin, leukocytes and thrombocytes, 1 hour erythrocyte sedimentation rate (ESR), and titer of C-reactive protein (CRP). The 24 hour urine creatinine clearance was measured and monitored. Serum creatinine and urate levels were monitored initially monthly, then every 3–6 months, and once a year after 2 years.

Hyperlipidemia was defined when the total cholesterol was  $> 200$  mg/dl and triglycerides  $> 150$  mg/dl. Impaired renal function was defined when the level of serum creatinine was  $> 2$  mg/dl (National Institutes of Health criteria) and/or creatinine clearance was  $< 60$  ml/min.

Obesity in Asians was defined as body mass index (BMI)  $> 23$ <sup>7</sup>.

Self-medication was defined when drugs were purchased and taken without medical supervision, often in incorrect dosage and frequency of administration over a shorter period than required.

*Treatment.* In those patients in whom self-medication had been insufficient acute gouty attacks at presentation were treated with nonsteroidal antiinflammatory drugs (NSAID) and/or corticosteroids. If this had insufficient effect intramuscular (IM) dexamethasone 10 mg and/or IM NSAID and/or methylprednisolone were given until the inflammation had diminished.

When arthritis persisted more than 2 weeks, a second dose of dexamethasone 10 mg IM (for the acute effect) and additionally depo-triamcinolone 40 mg IM (for longterm effect) was administered. Joints with persistent arthritis were given intraarticular injection with a joint-size-dependent dose of the combination of 2% lignocaine, dexamethasone, and/or depo-triamcinolone.

To prevent flare, low dose colchicine (0.5 mg) or low dose NSAID were administered for 6–24 months when urate-lowering drugs were started. Colchicine was stopped for prevention of flare when disease was controlled for at least 2 years. Omeprazole was provided to high-risk patients who had a history of moderate to severe gastroduodenal disorders to minimize gastrointestinal adverse effects<sup>8</sup> when oral NSAID plus

methylprednisolone or IM dexamethasone plus triamcinolone were administered (n = 76, 25.4%).

In Group 1, besides diet counselling, allopurinol and/or probenecid were initially given in therapeutic dosages and later in minimum effective maintenance doses for at least 2 years after attaining control of gout (benzbromaron is not available in Indonesia). After serum uric acid was controlled, allopurinol and/or probenecid were tapered. If a flare recurred after stopping urate-lowering drugs, these were resumed and continued on a longterm basis. Those who experienced no flare with diet controls and without urate-lowering drugs for at least one year were defined as being in control without treatment.

In Group 2, allopurinol was continued for the long term. A history of urolithiasis precluded the prescription of probenecid or other uricosurics. Longterm allopurinol was prescribed in the case of urolithiasis and/or tophi, and a lower dose in those with impaired renal function<sup>9,10</sup>. NSAID and/or corticosteroids were supplied to be taken in case of incipient flare. Incidentally, short term methylprednisolone was prescribed only in case of intolerance for NSAID and colchicine.

Also in Group 2, low dose NSAID or low dose corticosteroid or colchicine were prescribed for at least 6 months and if indicated up to 2 years to prevent flares of acute arthritis during subsequent reduction of serum uric acid concentration.

Patient education was given to all patients and supported by picture-leaflets for lay people, with information including joint protection during arthritis, advice for reduction of obesity, abstinence from alcohol, and a list of purine-rich food items to avoid. An interactive hotline by telephone, e-mail, and fax was established to report any untoward event within at most 1–2 days.

*Statistics.* Statistical analysis was performed using SPSS-PC v. 9 software.

The ethics committee of the university hospital of Semarang agreed to have the study performed.

## **RESULTS**

The original group consisted of 307 patients with chronic gout ([Table 1](#)). Excluded from the analysis were 8 men with gout plus another diagnosis of an autoimmune disease, leaving a total of 299 for the study. No cases with chondrocalcinosis were seen on radiographs ([Table 1](#)).

**Table 1.** Data of the cases at first and last visit including dropouts; data in percentages.

	Group 1, First Visit, n = 228	Group 2, First Visit, n = 71				
Mean age at onset of diseases $\pm$ SD, yrs	35 $\pm$ 7.2	34 $\pm$ 9.7				
Mean disease duration $\pm$ SD, yrs	9 $\pm$ 1.4	10 $\pm$ 1.8				
Mean no. of attacks/yr $\pm$ SD	4.2 $\pm$ 0.9	8.2 $\pm$ 3				
Synovial fluid aspirated, n (%)	23 (10.1)	70 (98.6)				
MSU crystals in synovial fluid, n (%)	15 (6.6)	52 (73.2)				
Normouricemic, n (%)	113 (49.6)	23 (32.3)				
		Final Visit, n	Dropouts, n		Final Visit, n	Dropouts, n
		176	52		62	9
Death		0	0		0	3
Lost to followup		0	1		0	1
Evaluated	228	176	51	71	62	5
BMI > 25 kg/m <sup>2</sup> , %	0.0	2.8	9.8	2.8	6.8	60.0
BMI > 23 kg/m <sup>2</sup> , %	10.1	9.7	54.9	50.7	52.5	80.0
Tophi, %	0.0	0.0	39.2	40.8	8.1	100.0
No. of tophi	0	0	26	127	17	49
No. of patients with tophi	0	0	8	29	5	5
History of urolithiasis, %	0.0	0.0	47.1	23.9	28.8	60.0
Serum creatinine > 2 mg/dl, %	0.0	0.0	25.5	33.8	6.8	60.0
Creatinine clearance < 30 ml/min, %	0.0	0.0	27.5	28.2	0.0	60.0
Triglycerides > 150 mg/dl, %	60.1	19.9	78.4	60.6	20.3	80.0
Cholesterol > 200 mg/dl, %	29.8	16.5	60.8	54.9	16.9	100.0
Blood pressure > 90/140 mm Hg, %	17.5	2.3	31.4	22.5	3.4	40.0
Fasting glucose > 140	0.0	0.6	3.9	5.6	1.7	40.0

mg/dl, %							
Transient ischemic attack, %	0.4	1.1	3.9	2.8	3.4	60.0	
Stroke, %	0.0	1.1	5.9	1.4	5.1	60.0	
Ischemic heart disease, %	0.0	1.1	5.9	12.7	3.4	80.0	

MSU: monosodium urate.

The education background of the patients was senior high school and higher. These subjects belonged to the upper middle and high social classes, and could afford longterm treatment of gout and hyperuricemia. They came to Semarang from all parts of Indonesia.

Diagnosis of gout was established in 67 cases with proven urate crystals in synovial fluid aspirate, and in 232 (77.6%) of the patients by careful application of the clinical criteria<sup>6</sup> (Table 1). There were no significant differences in Group 1 regarding baseline demographic, laboratory, and clinical features between the 15 cases of crystal-confirmed gout and the 213 cases of clinically-diagnosed gout (Table 2).

**Table 2.** Univariate analysis of mean scores  $\pm$  SD of primary endpoints of the same patients inclusive of dropouts between the first and last visit.

	First Visit			Last Visit			Baseline, Dropouts	Final Dropouts
	Group 1	Group 1	Group 2	Group 1	Group 1	Group 2		
	- Self	+ Self	+ Self	- Self	+ Self	+ Self		
Gout, n*	8	7	52	7	7	51	2	2
Evaluated in no. of patients	120	108	71	93	83	59	61	56
Uric acid $\leq$ 7 mg/dl, %	51.8	47.2	32.3	100.0	100.0	100.0	45.9	21.4
Serum UA, mg/dl	10.1 $\pm$ 2.6	10.7 $\pm$ 2.2	11.7 $\pm$ 2.9	4.6 $\pm$ 0.6	4.7 $\pm$ 0.7	4.9 $\pm$ 0.8	10.3 $\pm$ 1.5	11.9 $\pm$ 2.0
Serum urea, mg/dl	45.7 $\pm$ 7.8	50.9 $\pm$ 10.4	69.3 $\pm$ 17.9	35.4 $\pm$ 5.1	40.8 $\pm$ 7.7	41.2 $\pm$ 9.7	55.6 $\pm$ 10.6	59.3 $\pm$ 17.9
Proteinuria, 1-4+	2.1 $\pm$ 0.3	2.3 $\pm$ 0.4	2.6 $\pm$ 0.3	1.1 $\pm$ 0.2	1.1 $\pm$ 0.2	1.4 $\pm$ 0.2	2.3 $\pm$ 0.3	2.4 $\pm$ 0.3
Hematuria**	7.9 $\pm$ 2.1	12.8 $\pm$ 2.4	25.4 $\pm$ 4.7	4.4 $\pm$ 0.9	3.3 $\pm$ 1.1	1.1 $\pm$ 0.2	11.1 $\pm$ 3.2	24.4 $\pm$ 5.7
Creatinine, mg/dl	1.4 $\pm$ 0.2	1.7 $\pm$ 0.2	2.1 $\pm$ 0.7	0.8 $\pm$ 0.1	0.9 $\pm$ 0.1	0.9 $\pm$ 0.2	1.5 $\pm$ 0.2	2.4 $\pm$ 0.4
CrCI, ml/min	64.9 $\pm$ 15.9	53.4 $\pm$ 8.4	49.1 $\pm$ 13.7	82.1 $\pm$ 17.2	75.5 $\pm$ 15.9	71.9 $\pm$ 15.9	61.9 $\pm$ 15.6	48.6 $\pm$ 12.3
Triglyceride, mg/dl	193.8 $\pm$ 44.7	271.5 $\pm$ 52.7	378.8 $\pm$ 87.7	149.2 $\pm$ 39.4	148.3 $\pm$ 46.5	159.6 $\pm$ 53.5	243.5 $\pm$ 61.1	311.7 $\pm$ 73.4
Cholesterol, mg/dl	247.2 $\pm$ 53.7	269.9 $\pm$ 56.6	313.2 $\pm$ 62.5	199.9 $\pm$ 44.6	209.7 $\pm$ 53.1	221.9 $\pm$ 49.3	278.3 $\pm$ 50.5	314.6 $\pm$ 62.8
Fasting glucose,	99.2 $\pm$	124.7 $\pm$	139.8 $\pm$	81.2 $\pm$	89.4 $\pm$	90.7 $\pm$	105.3 $\pm$ 25.6	131.5 $\pm$

mg/dl	19.2	25.8	28.9	18.7	21.6	22.6		33.3
ALT, U/I	24.9 ± 4.7	45.7 ± 7.6	77.0 ± 19.3	7.7 ± 1.6	8.6 ± 1.2	9.4 ± 1.7	36.2 ± 12.2	47.0 ± 19.3

Self: self-medication; \* Crystal-confirmed gout. \*\* Patients with  $\geq 4$  erythrocytes per field. CrCl: creatinine clearance.

In Group 1, after 2 years 206 (of 228) patients were free of attacks, and urate-lowering drugs were tapered when uric acid levels had remained normal for 2 years and no gouty attacks had occurred, so they continued only the recommended diet. Out of these, 84 cases remained without flares over the following 8 years. Those who experienced flare always showed increased serum uric acid levels and urate-lowering drugs were resumed.

In Group 1, accounting for dropouts, 101 patients were still taking allopurinol and 12 were taking allopurinol plus probenecid at 5 years. At 10 years only 86 were taking allopurinol and 6 allopurinol plus probenecid. In Group 2, all subjects took only allopurinol until the final visit ([Table 3](#)).

**Table 3.** Treatment and control of hyperuricemia, dropouts, and flares in 299 men with chronic gout.

	N (%)	N (%)	N (%)
<b>Group 1, 228 patients</b>			
Cumulative duration therapy, yrs	2	5	10
Treated with allopurinol	206 (90.4)	101 (44.3)	86 (37.7)
Treated with allopurinol + probenecid	22 (9.6)	12 (5.3)	6 (2.6)
Without urate-lowering drugs	— (—)	84 (36.8)	84 (36.8)
Serum uric acid < 5 mg/dl	206 (90.4)	197 (86.4)	176 (77.2)
For period of, yrs	0–2	2–5	5–10
Dropouts, n	22 (9.6)	9 (4.4)	21 (10.7)
Number of flares	190	63	60
<b>Group 2, 71 patients, all treated with allopurinol only</b>			
Cumulative duration, yrs	2	5	10
Serum uric acid < 5 mg/dl	68 (95.8)	65 (91.5)	62 (87.3)
For period of, yrs	0–2	2–5	5–10
Dropouts, n	3 (4.2)	3 (4.4)	3 (4.6)
Number of flares	154	51	50

*Self-medication.* Sixty percent (n = 179) of patients, including all those of Group 2, had a history of previous intermittent self-medication for a mean of  $10 \pm 2.7$  years (Table 2). These medications, available without prescription, were "herbal" capsules or pills containing herbs plus prednisone, often combined with phenylbutazone or a drug package with a 3-day supply of prednisone plus phenylbutazone or diclofenac along with antacids taken 3 times daily. In Group 1, the baseline values of those with previous self-medication, triglycerides, cholesterol, fasting glucose, and liver and renal function were worse compared with those without self-medication at presentation (Table 2). In Group 2 (who had all been on self-medication), these laboratory variables were worse at baseline compared with the subgroups of Group 1. Deterioration of these laboratory variables was more pronounced over 10 years in the dropouts compared with the treated subjects of Groups 1 and 2.

Unadjusted p values from paired t tests of comparison of variables between baseline and final figures were  $< 0.0001$  to  $< 0.0005$  in Group 1 including its subgroups without and with self-medication, in Group 2, and in the dropouts between baseline and final visit (Table 2). Hyperuricemia and serum urea, proteinuria, hematuria, serum creatinine, and creatinine clearance improved significantly due to treatment and withdrawal of prednisone and NSAID. Renal function, serum cholesterol and triglycerides, fasting blood sugar, and liver function also improved significantly with concomitant therapy and the recommendation of a low purine, low fat, low calorie diet. The differences between the mean baseline and the mean final figures in the dropouts were significantly worse, as expected.

Patients who failed to suppress a prodromal attack of acute arthritis with 4 mg methylprednisolone TID on the first day were empirically provided the 16 mg tablets TID, which prevented almost all subsequent symptoms of acute gouty arthritis or flare.

Fifty-two dropouts came from Group 1 and 9 from Group 2 (Table 1). The dropouts were traced and data for 59 were collected from community health centers, outpatient clinics, and hospitals and by individual interviews. The reasons for dropout in 61 cases were termination of urate-lowering drug(s) in 44 (72%), and not showing up for scheduled laboratory monitoring and evaluation in 15 cases (25%). Only 51 dropouts from Group 1 and 5 from Group 2 were evaluated, due to loss of one dropout from each group and 3 deaths from Group 2 (Table 1). The 3 deaths were due to renal failure (one case, age 42), stroke (one case, age 47), and heart attack (one case, age 49).

The baseline variables of the traced dropouts from Group 2 showed a worse status compared with the dropouts from Group 1. The number of dropouts in Group 2 was too small for interpretation of a worse outcome compared with baseline. Outcomes of dropouts from Group 1 were significantly worse compared with baseline.

Flares were ascribed to noncompliance of daily intake of urate-lowering drugs and incidental overindulgence in purine-rich food, i.e., beer. In 5 cases flares were ascribed to the chronic use of diuretics, and in one to use of aspirin 80 mg daily.

Only 2.8% of cases in Group 2 had a BMI  $> 25 \text{ kg/m}^2$  (obesity) at the first visit. After 10 years, obesity had increased from 0.0% to 2.8% in Group 1 and in Group 2, from 2.8% to 6.5%. For both groups the increase of obesity (BMI  $> 25 \text{ kg/m}^2$ ) was from 0.7% to 3.8% (Table 1). Dropouts from Group 1 had 0.0% baseline obesity, but increased to 9.8%; and Group 2 at baseline had 2.8% obesity and increased to 60.0% at 10 years. When the cutoff point of  $> 23 \text{ kg/m}^2$  for obesity for Asians was applied, it was similar at baseline and after 10 years between Groups 1 and 2. In the dropouts, obesity increased in Group 1 from 9.6% to 54.9% and in Group 2 from 44.4% to 80%. Asian nutritionists are inclined to apply a limit of  $> 23 \text{ kg/m}^2$  for obesity due to lower stature and body weight<sup>7</sup>. This criterion classifies the majority of the patients in Group 2 with obesity (Table 4). By this criterion, the increase in the percentages of obesity in the cases was significantly reduced by treatment compared with the dropouts.

Maintaining a serum urate concentration of  $< 5 \text{ mg/dl}$  over the long term resulted in reduction of the number of tophi from 127 to 17 in Group 2. Only 5 patients from Group 2 still had tophi at the end of the study (Table 1). After 10 years, 26 new tophi appeared in the dropouts from Group 1. The number of tophi had increased from 18 to 49 in the dropouts from Group 2. In those who completed the treatment in Group 1, the development of tophi was prevented (Table 1). Twenty cases in Group 2 had their tophi dissolved, but the 5 evaluated dropouts who had multiple tophi and renal impairments at baseline had developed many new small tophi, and existing small ones developed into multiple large tophi.

No urolithiasis and no deterioration of renal function were recorded during 10 years in Group 1, when serum uric acid was kept at  $< 5 \text{ mg/dl}$  (Table 1). The percentage of patients in Group 2 with urolithiasis increased notwithstanding control of hyperuricemia from 23.5% to 28.8%. After 10 years of uncontrolled hyperuricemia, 47.1% of dropouts from Group 1 had urolithiasis. In Group II dropouts, the percentage with urolithiasis increased from 22.2% to 60.0% at the final evaluation. The percentage of patients with baseline serum creatinine  $> 5 \text{ mg/dl}$  in Group 2 decreased significantly after 10 years of control of hyperuricemia (Table 1), and the percentage of patients with creatinine clearance of  $< 30 \text{ ml/min}$  in Group 2 had decreased to zero.

The percentages of patients with triglycerides  $> 150 \text{ mg/dl}$ , cholesterol  $> 200 \text{ mg/dl}$ , and blood pressure  $> 140/90 \text{ mm Hg}$  in Groups 1 and 2 were reduced significantly after 10 years of control of hyperuricemia and concomitant therapy for complications and associated conditions when compared with baseline (Table 1). The percentages of these factors among the dropouts from Groups 1 and 2 after 10 years had increased significantly compared with baseline.

Incidental IM injections of dexamethasone and depo-triamcinolone did not induce serious adverse effects or dependency on corticosteroids<sup>11</sup>. No case of Stevens-Johnson syndrome due to allopurinol was encountered. Six patients with itching and urticaria were desensitized<sup>12</sup> while taking probenecid, and the hyperuricemia was subsequently controlled by longterm use of allopurinol.

## DISCUSSION

From this 10 year observation we concluded that chronic gout is a readily controllable disease even in a developing country. When symptoms of chronic gout and serum urate concentration remain under control over a period of 10 years, complications can be prevented along with associated conditions (Table 1). Maintaining a mean serum uric level of < 4.5–5.0 mg/dl is the optimal range to avoid a flare of acute arthritis<sup>13</sup>, and induces reduction of the number and size of tophi<sup>14</sup>, prevention of urolithiasis, and improvement of renal function and other associated conditions.

The possibility that urate-lowering drugs may have been included in the herbal treatments taken before the first visit in the cases and after dropout cannot be excluded. Flare of acute arthritis may occur in chronic gout in patients who are normouricemic<sup>15,16</sup>. Two recent studies report that the incidence of acute gouty arthritis was 39%<sup>17</sup> and 43%<sup>18</sup> among patients who were normouricemic. The observation in our series of normal uric acid levels in 47.2% of subjects in Group 1 and 51.8% in Group 2 suggests that Malayo-Polynesian men with chronic gout have a hyperuricemic upper normal value lower than 7 mg/dl.

Among the dropouts many complications developed and existing complications and associated conditions worsened, which led to disability and more severe morbidity and in some cases early death (Table 1). Our observations are compatible with findings from Japan that hyperuricemia has a strong association with relative risk of death in coronary heart disease, hypertension, stroke, liver disease, and renal failure, indicating that increased serum uric acid is a considerable risk factor for reduced life expectancy<sup>19</sup>. However, this has to be interpreted with caution, as the number of dropouts from our Group 2 is small. Early mortality appeared in a relatively high percentage in the dropouts, and in none of those where hyperuricemia was controlled (Table 1). Hyperuricemia is a risk factor for mortality in angiographically-proven coronary artery disease<sup>20</sup> and in stroke survivors<sup>21</sup>. Mortality may be ascribed to unsupervised ingestion of NSAID plus prednisone along with predisposition of the disease in associated conditions<sup>1</sup>.

The improvement of serum creatinine and creatinine clearance were impressive in Group 1 and Group 2 after longterm control of hyperuricemia and chronic gout when self-medication with NSAID and/or prednisone was terminated (Table 1). This improvement of renal function was similar to a study by Perez-Ruiz, *et al*, where hyperuricemia and gout were controlled for one year<sup>22</sup>. The impressive improvements of hypertension and hyperlipidemia cannot be ascribed solely to control of hyperuricemia and chronic gout, but were mainly due to blood pressure and lipid-lowering drugs and lifestyle recommendations of low salt, low fat, low purine diet.

In chronic gout without complications, 36.8% of subjects in Group 1 achieved treatment-free control over a period of 8 years (Table 3). However, this was impossible to achieve in those with clinically diagnosed and crystal-confirmed gout with complications in Group 2. Urate-lowering drugs also could not be tapered in patients with tophi, as acute arthritis will always flare sooner or later<sup>23,24</sup>. The explanation for normal uric acid levels

in these patients may be the following factors: the main staple food of Malayo-Polynesians is daily rice with vegetables, fruits, and sometimes wet and dry bean cake, but certainly no daily overindulgence in purine-rich foods such as beef and goat meat and offal comprising liver, kidney, brain, and intestines; alcohol consumption is negligible (0.03%) in Central Java<sup>1</sup>, and this may have made longterm compliance to a low purine diet less a problem compared with the Caucasian lifestyle and diet. It is apparently possible for many patients to refrain from drinking alcohol and eating a "western" diet.

The most popular herb mixture used in therapy of rheumatic disease in China and Taiwan has proven to be ineffective in acute gouty arthritis and does not lower uric acid levels<sup>25</sup>. Any herb capsule or satchel that is effective in the treatment of acute gouty arthritis and lowers serum uric acid should be suspected of containing illicit corticosteroid and/or NSAID and uricostatic and/or uricosuric compounds<sup>1</sup>.

Self-medication is immensely popular because these medications are accessible without prescription fees, cheap, and mostly effective in the acute arthritis of early gout. In this sample, 59.9% of the patients (Group 1, n = 108; Group 2, n = 71) had a 10 year history of previous self-medication without control of hyperuricaemia due to ignorance (Table 2). This figure is similar to that found in an epidemiological survey for self-medication<sup>1,26</sup>.

Exposure to longterm (10 years) intermittent or continuous prednisone in the dropouts as part of the self-medication, often up to 5 mg TID, may have increased existing or induced hypertriglyceridemia and hypercholesterolemia, but certainly hyperglucosemia in many cases (Tables 1 and 2), as is also seen during longterm treatment of systemic lupus erythematosus with high dose corticosteroid<sup>27</sup>.

The patients in Group 1 appeared to be less motivated to comply with daily intake of urate-lowering drugs and regular monitoring of serum urate levels, as suggested by a larger number of dropouts compared with Group 2 (Table 3). Literacy has facilitated patients' education in both groups<sup>28</sup>. In the patients of Group 2, who already had complications and associated conditions, patient education apparently induced a higher awareness of possible detrimental consequences of neglect. This may have motivated the patients to better compliance.

Corticosteroid is an effective alternative by the parenteral route when NSAID and colchicine cannot be tolerated or when gout becomes resistant to oral corticosteroids and oral or IM NSAID<sup>11,29</sup>. Intraarticular corticosteroid is effective in gouty joints resistant to systemic therapy<sup>30</sup>. Local administration of corticosteroid, i.e., with no net effects on bone resorption and only a systemic inhibition of bone formation lasting 14 days<sup>31</sup>. Only about 20% of intraarticular injected corticosteroids leak into the systemic blood circulation<sup>32</sup>. Intraarticular injection has less effect on bone metabolism than continuous oral corticosteroid when applied in acute arthritis in patients with longstanding gout<sup>31</sup>.

Flare of acute gout ascribed to diuretics during the first 2 years of therapy was found in only 5 cases with serum uric acid levels > 5 mg/dl in Group 2. Diuretic-induced gout

occurs only in patients in whom there is an additional cause for hyperuricemia, usually impaired renal function<sup>10</sup>.

Urolithiasis is associated with hyperuricosuria and gouty diathesis. Hyperuricemia and hyperuricosuria in tropical climates, where low urine volume and acid urinary pH promote precipitation of uric acid, may result in > 40% prevalence of urolithiasis<sup>33</sup>. The presence of urolithiasis in 23.9% of patients in Group 2 after one decade of disease duration is high. In spite of control of hyperuricemia the percentage of patients with urolithiasis in Group 2 increased in the second decade. Hyperuricemia (> 9 mg/dl) is only one of the many risk factors for development of urolithiasis. In this study, 48.2% of dropouts were affected by urolithiasis after a disease course of 2 decades, without longterm control of hyperuricemia (Table 1). Longterm urate-lowering drugs together with taking much fluid will reduce the number of kidney stones and prevent renal disorders. Although radiographs did not show chondrocalcinosis, pseudogout cannot be excluded in the 77.6% (Table 1) of cases where gout was clinically diagnosed without evidence of monosodium urate crystals. The figure will be very low, as the prevalence of chondrocalcinosis in Malayo-Polynesians is 1%<sup>34</sup> and the clinical picture in general is very different.

A real control group would be required to get a true picture of the natural course of the disease instead of the small number of dropouts, but in our opinion this is ethically unacceptable over a period of 10 years where irreversible complications and associated conditions of chronic gout are longterm risk factors for mortality.

In summary, if self-medication continues in a population with a high prevalence of gout, many cases of chronic gout will be seen, and the number of complications and associated conditions may increase and become a public health problem<sup>1</sup>. These factors may lead to severe disability, morbidity, and early mortality. Better control of gout was a success story in many Western countries, where chronic tophaceous gout is rare. This was only partly due to the availability of effective drugs. The benefits of control of chronic gout shown in this study are not yet appreciated in a developing country, even in the affluent patients.

By controlling hyperuricemia, complications and associated conditions may be prevented, the prognosis of chronic gout will improve, and comorbidity and early death will be prevented. If it continues unchecked, self-medication in a developing country may become a public health problem in a population with a high prevalence rate of gout.

## REFERENCES

1. Darmawan J, Valkenburg HA, Muirden KD, Wigley RD. The epidemiology of gout and hyperuricemia in a rural population of Java. *J Rheumatol* 1992;19:1595-9. [[MEDLINE](#)]
2. Darmawan J, Lutalo SK. Gout and hyperuricaemia. *Baillieres Clin Rheumatol* 1995;9:83-94. [[MEDLINE](#)]

3. Klemp P, Stansfield SA, Castle B, Robertson MC. Gout is on the increase in New Zealand. *Ann Rheum Dis* 1997;56:22-6. [[MEDLINE](#)]
4. Lawrence RC, Hochberg MC, Kelsey JL, et al. Evidence of the prevalence of selected arthritic and musculoskeletal diseases in the United States. *J Rheumatol* 1989;16:427-41. [[MEDLINE](#)]
5. Owen DS. A cheap and useful compensated polarizing microscope. *N Engl J Med* 1971;285:1152.
6. Wallace SH, Robinson H, Masi AT, Decker JL, McCarty DJ, Yu TF. Primary criteria for the classification of acute arthritis of primary gout. *Arthritis Rheum* 1977;20:895-900.
7. Singh RB, Rastogi SS, Rao PV, et al. Diet and lifestyle guidelines and desirable levels of risk factors for the prevention of diabetes and its vascular complications in Indians: a scientific statement of The International College of Nutrition. Indian Consensus Group for the Prevention of Diabetes. *J Cardiovasc Risk* 1997;4:201-8. [[MEDLINE](#)]
8. Russell AS, Darmawan J, Scott DL, Brooks PM, Hubscher O. Guidelines for use of antirheumatic drugs. *J Rheumatol* 1994;21:79-81. [[MEDLINE](#)]
9. Borg EJ, Rasker JJ. Gout in the elderly, a separate entity? *Ann Rheum Dis* 1987;46:72-6. [[MEDLINE](#)]
10. Scott JT, Higgins CS. Diuretic induced gout: a multifactorial condition. *Ann Rheum Dis* 1992;51:259-61. [[MEDLINE](#)]
11. Groff GD, Franck WA, Raddatz DA. Systemic steroid therapy for acute gout: a clinical trial and review of the literature. *Semin Arthritis Rheum* 1990;19:329-36. [[MEDLINE](#)]
12. Fam AG, Lewtas J, Stein J, Paton TW. Desensitization to allopurinol in patients with gout and cutaneous reactions. *Am J Med* 1992;93:299-302. [[MEDLINE](#)]
13. Yamanaka H, Togashi R, Hakoda M, et al. Optimal range of serum urate concentrations to minimize risk of gouty attacks during anti-hyperuricemic treatment. *Adv Exp Med Biol* 1998;431:13-8. [[MEDLINE](#)]
14. Perez-Ruiz F, Galabozo M, Pijoan PI, Herrero-Bettes AM, Ruibal A. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. *Arthritis Care Res* 2002;47:356-60. [[MEDLINE](#)]
15. McCarty DJ. Gout without hyperuricemia. *JAMA* 1994;271:302-3. [[MEDLINE](#)]
16. Logan JA, Morrison E, McGill PE. Serum urate during acute gout. *Br J Rheumatol* 1995;Suppl 2:34-40.

17. Logan JA, Morrison E, McGill PE. Serum uric acid in acute gout. *Ann Rheum Dis* 1997;56:696-7. [[MEDLINE](#)]
18. Schlesinger N, Baker DG, Schumacher HR Jr. Serum urate during bouts of acute gouty arthritis. *J Rheumatol* 1997;24:2265-6. [[MEDLINE](#)]
19. Tomita M, Mizuno S, Yamanaka H, et al. Does hyperuricemia affect mortality? A prospective cohort study of Japanese male workers. *J Epidemiol* 2000;10:403-9. [[MEDLINE](#)]
20. Bickel C, Rupprecht HJ, Blankenberg S, et al. Serum uric acid as an independent predictor of mortality in patients with angiographically proven coronary artery disease. *Am J Cardiol* 2002;89:12-7. [[MEDLINE](#)]
21. Wong KY, Macwalter RS, Fraser HW, Crombie I, Ogston SA, Struthers AD. Urate predicts subsequent cardiac death in stroke survivors. *Eur Heart J* 2002;23:788-93. [[MEDLINE](#)]
22. Perez-Ruiz F, Calabozo M, Herrero-Beites AM, Garcia-Erauskin G, Pijoan JI. Improvement of renal function in patients with chronic gout after proper control of hyperuricemia and gouty bouts. *Nephron* 2000;86:287-91. [[MEDLINE](#)]
23. van Lieshout-Zuidema MF, Breedveld FC. Withdrawal of long-term antihyperuricemic therapy in tophaceous gout. *J Rheumatol* 1993;20:1383-5. [[MEDLINE](#)]
24. Bull PW, Scott JT. Intermittent control of hyperuricemia in the treatment of gout. *J Rheumatol* 1989;16:1246-8. [[MEDLINE](#)]
25. Chou CT, Kuo SC. The anti-inflammatory and anti-hyperuricemic effects of Chinese herbal formula danggui-nian-tong-tang on acute gouty arthritis: a comparative study with indomethacin and allopurinol. *Am J Chin Med* 1995;23:261-71. [[MEDLINE](#)]
26. Darmawan J, Valkenburg HA, Muirden KD, Wigley RD. Epidemiology of rheumatic diseases in rural and urban populations in Indonesia: a World Health Organization–International League Against Rheumatism COPCORD study, stage I, phase 2. *Ann Rheum Dis* 1992;51:525-8. [[MEDLINE](#)]
27. Petri M, Spence D, Bone LR, Hochberg MC. Coronary artery disease risk factors in the Johns Hopkins Lupus Cohort: prevalence, recognition by patients, and preventive practices. *Medicine Baltimore* 1992;71:291-302. [[MEDLINE](#)]
28. Darmawan J, Valkenburg HA, Muirden KD, Wigley RD. Arthritis community education by leather puppet (wayang kulit) shadow play in rural Indonesia (Java). *Rheumatol Int* 1992;12:97-101. [[MEDLINE](#)]

29. Werlen D, Gabay C, Vischer TL. Corticosteroid therapy for the treatment of acute attacks of crystal-induced arthritis: an effective alternative to nonsteroidal antiinflammatory drugs. *Rev Rheum Engl Ed* 1996;63:248-54. [[MEDLINE](#)]
30. Rosenthal AK, Ryan LM. Treatment of refractory crystal-associated arthritis. *Rheum Dis Clin North Am* 1995;1:151-61. [[MEDLINE](#)]
31. Emkey RD, Lindsay R, Lyssy J, Weisberg JS, Dempster DW, Shen V. The systemic effect of intraarticular administration of corticosteroid on markers of bone formation and bone resorption in patients with rheumatoid arthritis. *Arthritis Rheum* 1996;39:277-82. [[MEDLINE](#)]
32. Gray RG, Tenenbaum J, Gottlieb NL. Local corticosteroid treatment in rheumatic disorders. *Semin Arthritis Rheum* 1981;10:231-54. [[MEDLINE](#)]
33. Levy FL, Adams-Huet B, Pak CYC. Ambulatory evaluation of nephrolithiasis: update of a 1980 protocol. *Am J Med* 1995;98:50-9. [[MEDLINE](#)]
34. Darmawan J. Rheumatic conditions in the northern part of Central Java. An epidemiological survey [PhD thesis]. Rotterdam: Erasmus University; 1988, 178 p.