

# Characteristics of Chronic Gout in Northern Sulawesi, Indonesia

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**ABSTRACT. Objective.** To identify associations and possible risk factors for gout that may contribute to chronic tophaceous gout in rural and urban districts of North Sulawesi, Indonesia.

**Methods.** A total of 190 patients with chronic gout and 190 age and sex matched controls were selected from 28 community health centers. Potential risk factors including alcohol consumption, food habits, family history, body weight, related medical conditions, drug use, and laboratory investigations were sought.

**Results.** Alcohol consumption and certain food habits were associated with gout. A positive family history of gout and overweight were also significant risk factors. Renal impairment was found in 86.3% of patients and hyperuricemia in 92.1%. In controls, renal impairment and hyperuricemia were 7.4% and 32.6%, respectively. Patients with hypertension and nephrolithiasis were more at risk of having associated gout. There was a significant association between gout, hyperuricemia, hypercholesterolemia, hypertriglyceridemia, and higher levels of creatinine and urea. There was also a significantly lower level of urine uric acid in gout cases compared with controls. Gouty tophi were found in 91% of these cases with chronic gout. The use of diuretics for treating hypertension, continuing excessive alcohol consumption and purine-rich food habits in untreated gout, and hyperuricemia were associated with chronic and tophaceous gout. Urate-lowering drugs were not available in the community health centers.

**Conclusion.** Severe tophaceous gout with deformities and disability is found in North Sulawesi. Prominent risk factors include alcohol, obesity, renal impairment, diet, hypertension, and family history. Improved education about gout seems needed. Urate-lowering drugs are not available in community health centers but are needed, especially in rural areas, as studied here. (J Rheumatol 2006;33:1813-7)

## Key Indexing Terms:

CHRONIC TOPHACEOUS GOUT      RISK FACTORS      INDONESIA      EPIDEMIOLOGY

A study in Ujung Pandang, South Sulawesi, Indonesia, and a survey in Bandung, Northern Central Java, showed that the prevalence of gout and hyperuricemia in residents in these areas was significantly higher than in Caucasians<sup>1,2</sup>. The research suggested that gout was a common arthritic condition in ethnic groups of the Malayo-Polynesian and Malayo-Mongoloid races<sup>2</sup>. Our population falls within the former group. Important associations with and potential risk factors for the development of hyperuricemia and gout have been identified. These include male sex, family history, obesity, chronic alcohol abuse, hypertension, diuretic use, increased body mass index, high triglyceride blood levels, and renal insufficiency<sup>1-3</sup>. In addition, The Johns Hopkins Precursors Study suggested that weight gain and the development of hypertension during the period of observation were important risk factors for the development of gout in Caucasian men<sup>4</sup>. A large number of epidemiological studies have found a clear

association between increased body weight and hyperuricemia, and this association is reinforced by the currently familiar picture of a patient with gout as a person who is significantly obese<sup>1,5</sup>. Among 21 young patients (14 men and 7 women, mean age 28 yrs) referred for precocious onset of gout and/or hyperuricemia, most patients had a family history of gout, and 14 of 21 had mild renal insufficiency<sup>6</sup>.

Patients have often presented too late for effective treatment when chronic tophaceous gout has led to irreversible deformities and disabilities<sup>1,2</sup>. This has been attributed to lack of information among patients and primary healthcare professionals, and, in Indonesia, to lack of availability of urate-lowering drugs in community health centers (CHC). More than 50% of patients have observed tophi for 7 to 9 years before presenting for treatment<sup>1</sup>. In the USA and New Zealand there was a 3-fold increase in the prevalence of gout over the past 2 decades<sup>5,7,8</sup>. The marked morbid and economic impact of protracted disease warrant more studies into effective control of gout and hyperuricemia. Our objective was to identify the possible risk factors for gout that may contribute to chronic tophaceous gout in a population in North Sulawesi.

## MATERIALS AND METHODS

One hundred ninety patients with chronic gout attending 28 CHC from urban and rural districts were identified by physicians and nurse investigators in the CHC. Chronic gout was defined when patients had  $\geq 3$  attacks of gout annually and/or when a tophus or tophi were present (Figures 1 and 2). Age and

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sex matched controls with no history of joint pain were selected from neighbors and friends from the same area as the patients. Relatives were excluded. Clinical gout was diagnosed by the principal investigator based on American College of Rheumatology 1987 preliminary criteria for gout<sup>9</sup>.

A case-control study was carried out to determine possible risk factors that may contribute to development of tophaceous gout. The principal investigator, laboratory assistant, nurse interviewer, and local internal medicine physician carried out interviews, obtained blood samples, and examined all the patients with suspected chronic gout. These procedures were completed within 3 months.

All patients who met the criteria for chronic gout were interviewed by a nurse interviewer, and blood samples were taken by a laboratory assistant. The frequency of alcohol intake and food habits were obtained by the modified recall method. Frequency was categorized as: every day, 2 or 3 times a week, once a week, less often than once a week, and never. Purine intake was recorded based on 6 categories: seafood, offal, meat, meat extracts, fruits, and legumes. Offal comprised liver, kidney, brain, and intestines. Soto is a popular rice soup made from an extract of shellfish, which includes a mixture of offal. The alcoholic beverage was fermented from palm sugar and distilled; yeast was not used in the fermentation.

Patients were questioned on intake of drugs that might affect uric acid metabolism or precipitate or alleviate gout attacks. Such drugs consisted of diuretics, aspirin, prednisone, nonsteroidal antiinflammatory medications, colchicine, and allopurinol. A history of the source of pain relief or other tablets usually taken by patients for the acute attack was also noted. Patients were asked to bring their drugs to the survey, and nurses identified the drugs used by each individual. Similar procedures were adopted for controls.



Figure 1. A typical large knee tophus.



Figure 2. A patient with olecranon and finger tophi.

Diseases associated with hyperuricemia and gout including hypertension, renal disease, coronary disease, diabetes mellitus, and others were recorded. All subjects had blood sugar measurements. Questions relating to these additional medical conditions were asked by the principal investigator. The family history of patients with gout and controls was recorded, seeking genetic and/or familial associations for the gout. The age of patients when they experienced the first attack of gout was categorized as 15–24, 25–34, 35–44, and > 44 years. Histories of shed stones in the urine, hematuria, and episodes of renal colic were recorded in the interview. No kidney stones were analyzed. Body weight was determined with a standardized scale (kg) and height (cm) was measured in the standing position, back against the wall, and looking straight ahead. Body weight was classified based on the formula:

$$\text{Ideal weight (kg)} = (\text{height} - 100 \text{ cm}) \pm 10\%$$

Patients were considered overweight if they were 10% over the ideal weight and underweight if 10% less than ideal weight. Hypertension was recorded when either systolic or diastolic blood pressure was > 140/90 mm Hg. A World Health Organization standardized laboratory of the Department of Health analyzed serum uric acid, creatinine, urea, cholesterol, triglyceride, and 24-hour urinary uric acid. Uric acid levels were determined by the enzymatic method.

*Statistical method.* Data analysis was done using conditional logistic regression, Egret version 0.9. The logistic regression model analyzed the individual and combined effects of a set of variables on the risk of disease.

## RESULTS

Patients with chronic gout consumed alcohol, seafood, offal, and meat significantly more frequently than controls (Table 1). More than 50% of patients consumed locally brewed alcohol (captikus) every day, and another 21.6% had this drink more than once a week.

A family history of gout was recorded in 61.6% of patients with gout and only 10% of controls. There was significantly more gout in any relative or male relatives of patients with gout than in controls (Table 2).

Overweight was found in 53.2% of cases and 32.1% of controls, while underweight was noted in 12.6% of cases and 47.9% of controls. Being overweight increased the risk of gout with an odds ratio of 2.40 (95% CI 1.55–3.72;  $p < 0.0001$ ).

Hypertension and nephrolithiasis were significantly more frequent in patients with gout compared with controls (Table 3). The number of patients with chronic heart diseases and diabetes mellitus were not significantly different between those with gout and controls. This might be due to small numbers of subjects with these diseases, as there were trends suggesting associations.

Laboratory analyses (Table 4) showed that cholesterol levels (normal range 150–250 mg%) were increased in 145 (76.3%) gout patients, while high triglycerides (normal range 40–160 mg%) were found in 173 (91.1%). Creatinine (normal range 0.6–1.1 mg%) was elevated above 1.1 mg% in 164 (86.3%) patients and urea levels (normal range 20–45 mg%) were  $> 45$  mg% in 69 (36.3%). Uric acid levels  $> 7.0$  mg% (normal range 3.4–7.0 mg%) were found on those single determinations in 175 (92.1%) patients with chronic gout. Twenty-four-hour urine uric acid levels were  $< 400$  mg in 137 (72.1%) patients (normal range 400–600 mg). There was a significant association of clinical gout with hyperuricemia, low 24-hour urinary uric acid, hypercholesterolemia, hypertriglyceridemia, and high levels of creatinine and urea compared with controls.

## DISCUSSION

Gout has been recognized for many years by the community in North Sulawesi. However, gout was thought of as a condi-

tion that would develop inevitably in almost every person, especially in men. Gout would only be seen as a problem when disability developed and patients become dependent upon their families.

Daily alcohol consumption has been a habit among this community for many generations. Although subjects may realize that their gout attacks were most probably triggered by alcohol, they often continued drinking due to habit, tradition, or addiction. Alcoholism was initially denied, and persistent questioning was required to confirm levels of use. Excessive alcohol consumption causes lactic acidosis, with decreased urate excretion and overproduction of uric acid that could both contribute to the hyperuricemia and development of gout seen in our patients<sup>4,10–13</sup>. Table 1 shows that alcohol was a risk factor for the development of gout in this population.

Hydrochlorothiazide, a diuretic, is the main drug used in CHC for the control of hypertension. Longterm diuretic therapy used for hypertension reduces renal excretion of urate. Thiazide diuretics are the drugs implicated most often in the induction of hyperuricemia<sup>14,15</sup>. However, a study of diuretic-induced gout suggested that this occurs only in patients in whom there is an additional cause for hyperuricemia, usually impaired renal function<sup>16</sup>. The strong familial distribution of gout in South Sulawesi is confirmed by our study in North Sulawesi<sup>1</sup>. A family history of gout, even though it is one generation removed, is significant in the expression of gout<sup>12,15</sup> compared with controls (Table 2). A review of 5 published series suggests that the familial incidence of gout averaged 20% among hyperuricemic relatives of gouty patients<sup>15</sup>. The genetic risk factor was considered to be autosomal-dominant<sup>15,16</sup>. In this study genetic and environmental risk factors cannot be separated, although familial clustering was confirmed.

The majority of patients were overweight compared with controls, as also previously noted<sup>17</sup>. Excessive body weight is

Table 1. Alcohol and food habits of patients with gout and controls (N = 190). The daily consumption of alcohol and certain foods was associated with an increased risk of gout.

Variables	Daily vs Never, OR (95% CI)	< Daily vs Never, OR (95% CI)	Ever vs Never, OR (95% CI)
Alcohol	7.71 (3.86–15.52)	1.62 (0.87–3.02)	2.95 (1.66–5.29)
Seafood	4.40 (1.39-inacc)	1.93 (1.12–3.33)	2.04 (1.19–3.50)
Offal food	3.60 (0.95-inacc)	1.95 (1.01–3.79)	2.01 (1.05–3.88)
Meat extract	2.08 (0.55–7.99)	2.26 (1.08–4.82)	2.26 (1.07–4.79)
Meat	23.22 (2.35-inacc)	11.00 (1.45-inacc)	11.61 (1.54-inacc)

inacc: inaccurate

Table 2. Family history of gout (N = 190). Data reveal that having a male relative with gout was a significant risk factor, and there was significantly more gout in relatives of gout patients than in controls.

Family Member with Gout	Gout, n (%)	Control, n (%)	OR (95% CI)	p
Female relatives	12 (6.4)	10 (5.3)	1.21 (0.48–3.12)	$> 0.5$
Male relatives	90 (47.4)	9 (4.8)	18.10 (8.40–40.28)	$< 0.0001$
Any relatives	117 (61.6)	19 (10)	14.42 (8.01–26.23)	$< 0.0001$

**Table 3.** Related medical conditions in gout cases and controls. Cases with hypertension and nephrolithiasis were more at risk of being associated with gout. Although coronary heart disease and diabetes mellitus were not significantly different between gout cases and controls, this might be due to small numbers of subjects with these diseases, as there were trends suggesting associations.

Variable	Gout, n (%)	Controls, n (%)	OR (95% CI)	p
Hypertension	43 (22.6)	19 (10.0)	2.63 (1.42–4.92)	< 0.005
Coronary heart disease	12 (6.3)	8 (4.2)	1.53 (0.57–4.22)	NS
Diabetes mellitus	11 (5.8)	5 (2.6)	2.27 (0.71–inacc)	NS
Nephrolithiasis	25 (13.2)	8 (4.2)	3.45 (1.43–8.56)	< 0.005

NS: nonsignificant.

**Table 4.** Laboratory findings of gout cases and controls. There was a significant association between gout, hyperuricemia, hypercholesterolemia, and hypertriglyceridemia and higher levels of creatinine and urea. There was a significantly lower level of urine uric acid in gout cases compared with controls.

Variable	Gout, mean (SD)	Controls, mean (SD)	OR (95% CI)	p
Cholesterol	283.56 (52.20)	182.68 (42.26)	58.00 (27.0–127.84)	< 0.0001
Triglycerides	230.28 (60.28)	111.37 (42.87)	70.39 (34.89–144.25)	< 0.0001
Creatinine	1.90 (1.01)	1.05 (0.22)	79.30 (38.19–167.72)	< 0.0001
Urea	42.74 (21.62)	28.73 (9.83)	12.97 (5.77–30.30)	< 0.0001
Uric acid	9.07 (1.85)	6.36 (1.45)	24.09 (12.65–46.51)	< 0.0001
24-hour urine uric acid	339.2 (161.9)	621.99 (176.04)	20.80 (11.58–37.69)	< 0.0001

confirmed as a significant risk factor for the development of gout. Some underweight patients also showed multiple tophi and kidney disease in this series. This was also the case in an underweight rural sample population in Northern Central Java with gout and hyperuricemia<sup>2</sup>, and these findings cannot be explained by published observations. Starvation with acidosis has been reported to raise serum uric acid.

Hypertension and kidney stones have a significant association with gout. Hypertension can be due to kidney disease secondary to primary gout. Excessive alcohol consumption may be a factor causing both hyperuricemia and hypertension<sup>12</sup>.

Kidney disease remains a frequent association of gout and hyperuricemia, and is less likely to be manifested in patients given adequate treatment<sup>18</sup>. As hyperuricemia in our cases was untreated and most patients had never received any urate-lowering drugs, some renal impairment was regarded as being secondary to longterm untreated hyperuricemia or to hypertension or diabetes. Longterm uncontrolled hyperuricemia is an obvious risk factor in the development of chronic gout and multiple tophi. High creatinine levels were found in most gout cases, indicating that renal impairment was frequently present in the sample cases (Table 4) compared with controls. Time sequences of abnormalities cannot be established by these studies at one point in time.

Kidney disease in these patients might be due in part to urate deposits within the renal interstitium or due to uric acid stones<sup>19</sup>. Other renal diseases were not identified due to limited facilities in the CHC to determine diagnosis of other specific diseases. Although terminal renal insufficiency has long been implicated as a common cause of death in gout<sup>16,20</sup>, it

remains an open question whether the hypertension and renal disease are secondary to gout or whether patients suffer from primary renal disease with tophaceous gout.

Gout has been identified as a marker for susceptibility to coronary heart disease (CHD) in several studies<sup>21–23</sup>. In our cases CHD was not identified as a significant association with gout. Nevertheless, CHD may not be diagnosed due to lack of facilities and expertise, and consequent failure to interpret chest pain as due to angina pectoris. Similarly, diabetes mellitus was not associated with gout in this sample of patients; the reasons for this are unknown.

Phenylbutazone, methampyrone, prednisone, and other pain killers bought “over the counter” were frequently used by gout patients for relief of pain of acute attacks. This unsupervised, intermittent use of drugs for relief of pain may also have contributed to renal impairment<sup>20</sup>. Thiazides were the only drugs available for treatment of hypertension. The high prevalence rates of hyperuricemia and gout in male and female Polynesians, and Malayo-Polynesian men, compared with Caucasians<sup>20</sup> has been mostly attributed to underexcretion of uric acid<sup>24</sup>. The underexcretors may in fact have a normal rate of urinary uric acid excretion but require a higher serum uric acid to maintain this, as there is reduced efficiency of urate excretion. Thus, hyperuricemia and gout in these patients can be due to reduced efficiency of urate excretion by the kidneys.

Some families with primary gout have exhibited a reduced renal excretory capacity for urate, and these cases can be regarded as having primary gout of renal origin<sup>25</sup>. Underexcretion of urate in our cases can be due to primary



renal impairment. Several studies showed that in a gouty population several aspects of kidney function may be significantly impaired. Other studies indicate that gout might be the primary cause of renal disease<sup>16,20,26</sup>. The decreased fractional excretion of uric acid and the observed increased frequency of HLA-B14<sup>27</sup> suggest possible racial or genetic predisposition of gout and hyperuricemia, and call for further biomolecular studies in Malayo-Polynesian and Malayo-Mongoloid peoples.

Results of this and other studies reveal that chronic tophaceous gout is a significant public health problem in Sulawesi. Population surveys show that the prevalence rate in Malayo-Polynesians is high in male adults (urban 4.8% and rural 1.7%). Continuing medical education is required for primary health professionals and patients. Effective educational efforts may reduce alcohol consumption. This may prevent, slow, or prevent worsening of chronic tophaceous gout. The lead content of local alcohol should be investigated, as lead pipes may have been used for distillation of captikus and lead poisoning cannot be excluded. Obesity should be prevented if possible. Thiazide diuretics for treatment of hypertension might be replaced with other antihypertension measures in CHC serving Malayo-Polynesian and Malayo-Mongoloid communities. Availability of a urate-lowering drug such as allopurinol in CHC is needed for control of gout and hyperuricemia and prevention of chronic tophaceous gout with all its consequences. The costs of all these interventions remain a major concern.

Severe tophaceous gout with deformities and disability is frequently found in North Sulawesi, especially in rural areas, due at least in part to lack of urate-lowering drugs. Possible risk factors for gout in this region identified in our study were excessive alcohol consumption, a certain dietary pattern, a positive family history, high body weight, and associated medical conditions including hypertension and renal impairment. Renal impairment was frequently found, and it remains uncertain whether gout is primary or secondary to primary kidney disease. Longterm hyperuricemia and untreated gout frequently cause large and multiple tophi leading to deformities and disability. Patient and community and health worker education is essential to help control this significant public health problem, and appropriate drugs for treating gout need to be made available in CHC as a matter of some urgency.

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