Comparison of the prevalence of hyperuricemia in families of patients with and without gouty arthritis among Balinese people

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ABSTRACT

Background: Gout is a metabolic disorder caused by hyperuricemia, which results from changes in uric acid metabolism. Both internal (e.g., genetics) and external factors (e.g., diet, habits, comorbidities) play role in the occurrence of hyperuricemia and the difference of hyperuricemia prevalence in different populations.

Objective: To compare the prevalence of hyperuricemia in families of gout and non-gout patients among Balinese people.

Methods: This cross-sectional study was carried out at the rheumatology clinic at Sanglah Hospital, Denpasar. Samples were collected using consecutive method and consisted of gout and non-gout patients. Several characteristics (alcohol and purine consumption, medications, blood pressure, body mass index, serum uric acid level, and serum creatinine) in both groups were collected and compared. Family members (first-degree relatives) of patients in each group were also recruited and had their serum uric acid level measured and compared.

Results: A total of 46 patients and 116 family members (23 patients and 58 family members in each group) were enrolled. Among gout patients, there was significantly higher prevalence of hyperuricemia, serum uric acid level, blood pressure, and serum creatinine; and lower creatinine clearance compared with the non-gout patients. There was significantly higher prevalence of hyperuricemia among families of gout patients compared with families of non-gout patients (60.3 vs. 29.3%, respectively; $p = 0.001$), with a prevalence ratio of 2.06. Mean serum uric acid level of the family members of gout patients were also significantly higher than the family members of non-gout patients (7.24 (SD 1.74) vs. 5.92 (SD 1.63) mg/dL, respectively; $p = 0.000$).

Conclusion: Among Balinese people in this study, significantly higher prevalence of hyperuricemia and mean serum uric acid level was observed in families of gout patients compared with families of non-gout patients.

Hyperuricemia (also known as uricacidemia, hyperuricacidemia, or uricemia) is a condition characterized by an increase in the serum uric acid level.[1] Hyperuricemia is defined as serum uric acid level of more than 7 mg/dL (6 mg/dL for female).[2] Uric acid is produced from the conversion of xanthine, an end-product of purine metabolism.[3] This substance, which was discovered in 1776 by Schele, is a white crystal that has no taste or odor and undergo degradation in high temperature into hydrogen cyanide. It has low solubility in water but is soluble in glycerin or alkaline solutions, a principle that is used in urine alkalinization to prevent urate stones formation. Due to the lack of uricase enzyme in human body, uric acid could not be further catabolized into more soluble compound.

Causes of hyperuricemia can be primary of secondary, and are related to the formation and metabolism of uric acid, which are influenced by endogenous (e.g., gender, age, genetics, presence of obesity, hypertension, kidney disease, or myeloproliferative disorders) as well as exogenous factors (e.g., diet, medications, alcohol consumption, or activity).[4] Genetic variance or defects may cause disturbance in uric acid metabolism, such as an increase in production, decrease in excretion, or the combination of both.[5] Exogenous factors account for 15% of the incidence of gout.[6]

Gout is a group of heterogeneous diseases that occur as a result of the deposition of monosodium urate crystals due to supersaturation of extracellular fluid with uric acid.[7] A small proportion (<5%) of uric acid binds with plasma protein, while the majority (~98%) of uric acid in plasma and other extracellular fluid exists in the form of monosodium urate at pH 7.4. Plasma is saturated with monosodium urate at a concentration of 6.8 mg/dL at 37°C. In higher concentration (i.e., hyperuricemia), there will be supersaturation of plasma with uric acid, thereby increasing the possibility of urate crystal precipitation.[8] This crystal deposition will induce gout. The clinical manifestations of gout depend on the location of monosodium urate crystal deposition: gouty arthritis when it is deposited in joints, formation of tophus/i or tenosynovitis when deposited in soft tissue, and formation of urate stones when deposited in urinary tract, which may lead to kidney failure.[9]

There are different underlying genetic mechanisms in hyperuricemia and gout;[10] however, the positive correlation between hyperuricemia and gout has been known.[11] Epidemiological studies had shown that the majority of gout patients have hyperuricemia, although around 15% of individuals

without gout also have hyperuricemia.[12] In Indonesia, populations in Northern and Southern Sulawesi as well as in Northern and Western Sumatra have high prevalence of hyperuricemia, which is regarded to occur as a result of genetic influences.[12] In previous studies in Bali, there was a high prevalence of hyperuricemia in families with history of gout, particularly among men. In a study that involved 64 family members of 18 patients with gouty arthritis, hyperuricemia was detected in 17 individuals (26.6%); frequency of hyperuricemia in male siblings was 41.6%, male offsprings 39.1%, and female offsprings was 5.0%.[7]

The aim of this study is to evaluate whether there is significant difference in the prevalence of hyperuricemia in families of gout and non-gout patients in Balinese population.

METHODS

Study design and patients

This cross-sectional study was conducted at the rheumatology clinic at Sanglah Hospital, Denpasar, Bali between July and November 2008. Samples were collected using consecutive method. Gout patients older than 12 years old who were diagnosed based on the 1977 American College of Rheumatology criteria for gouty arthritis were recruited. As a control group, patients with diagnosis other than gouty arthritis were also enrolled. Patients who had no family member, or had chronic kidney disease stage IV–V or myeloproliferative disorders were excluded from the study. Family members (first-degree relatives older than 13 years old) of each group were subsequently recruited and had their serum uric acid level measured. All participants gave consent to be enrolled in this study.

Assessment

Several clinical and demographic data were collected from the patients: age, height, weight, blood pressure, history of alcohol drinking, medications, diet history, serum uric acid level, and serum creatinine. Serum uric acid level of the family members was also measured. Obesity was defined as body mass index of ≥25 kg/m^2. Alcohol drinker was defined as having history of at least one drink of alcoholic beverage in the last 1 month. One standard drink in this study was defined as any alcoholic beverage that contains 10 g of ethanol (1 mL ethanol = 0.79 g).[13] Medications were defined as drugs that may affect serum uric acid level: low-dose aspirin (<2 g/day), diuretics (thiazide, furosemide), antituberculosis drugs (pyrazinamide, ethambutol), and uric acid-lowering drugs (allopurinol, probenecid). High-purine diet was defined as consumption of >300 mg purine per day. Diet history was assessed using a semiquantitative food frequency questionnaire, the data of which was used to calculate the amount of purine consumption per day (in mg/day), using a method that had been validated (κ coefficient = 0.816) in a previous study[14] in Denpasar. Hyperuricemia was defined as serum uric acid of more than 7 mg/dL (male) or 6 mg/dL (female). Hypertension was defined as systolic pressure of ≥140 mmHg or diastolic pressure of ≥90 mmHg.

Statistical analysis

Differences between the two groups were analyzed by χ^2 or Fisher's exact test as appropriate (for categorical variables), or by unpaired t-test or Mann-Whitney U test as appropriate (for numerical variables). A p value <0.05 was considered as significant. Additionally, prevalence ratio of hyperuricemia among the family members of the two groups was also calculated.

RESULT

Patients

Forty six patients (23 in each group) were enrolled in this study. From analysis we found that patients with gout had significantly higher prevalence of hyperuricemia, serum uric acid level, blood pressure, and serum creatinine; and lower creatinine clearance (table 1) compared with non-gout patients.

Table 1 Characteristics of patients

Characteristics	Gout (n = 23)	Non-gout (n = 23)	p Value
Age, years, mean (SD)	49.96 (8.10)	49.52 (7.66)	0.853
Male, n (%)	22 (95.70)	22 (95.70)	1.000
Obesity, n (%)	15 (65.22)	13 (56.52)	0.763
Body mass index, kg/m^2	25.78 (12.86)	25.33 (12.30)	0.750
Alcohol drinker, n (%)	0 (0)	1 (4.30)	1.000
On medications, n (%)	0 (0)	1 (4.30)	1.000
High-purine diet, n (%)	2 (8.70)	0 (0)	0.489
Amount of purine consumption, mg/day	104.50 (337.23)	69.75 (199.99)	0.132
Hyperuricemia, n (%)	20 (86.96)	9 (39.13)	**0.002**
Serum uric acid level, mg/dL, mean (SD)	8.67 (1.72)	6.88 (1.23)	**0.000**
Hypertension, n (%)	11 (47.83)	6 (26.09)	0.222
Systolic pressure, mmHg	140.00 (60.00)	120.00 (50.00)	**0.001**
Diastolic pressure, mmHg	90.00 (20.00)	80.00 (40.00)	**0.012**
Serum creatinine, mg/dL, mean (SD)	1.39 (0.44)	1.07 (0.18)	**0.003**
Creatinine clearance (calculated), mL/min	62.90 (126.90)	82.50 (97.17)	**0.018**

When not indicated, values are presented as median (range); statistically significant results are in boldface.

Family members

A total of 116 family members (58 in each group) were enrolled in this study. The prevalence of hyperuricemia was significantly higher in family members of gout patients compared with family members of non-gout patients (60.3 vs. 29.3%, respectively), with a prevalence ratio of 2.06. Table 2 describes the characteristics of family members in more detail.

Table 2 Characteristics of the family members

Characteristics	Gout (n = 58)	Non-gout (n = 58)	p Value
Age, years	40.62 (17.98)	41.45 (15.08)	0.789
Male, n (%)	41 (70.7)	36 (62.1)	0.432
Hyperuricemia, n (%)	35 (60.3)	17 (29.3)	**0.002**
Serum uric acid level, mg/dL			
Men	7.57 (1.82)	6.82 (1.30)	**0.043**
Women	6.44 (1.25)	4.43 (0.82)	**0.000**
Overall	7.24 (1.74)	5.92 (1.63)	**0.000**

When not indicated, values are presented as mean (SD); statistically significant results are in boldface.

When the family members were further classified and compared based on family relation and gender, we found that serum uric acid level was consistently higher in family members of gout patients (table 3).

Table 3 Serum uric acid level (mg/dL) in family members

Relationship	Gout		Non-gout	
	N	Mean (SD)	n	Mean (SD)
Parents				
Father	4	7.37 (2.40)	3	6.26 (1.30)
Mother	1	7.90	5	4.48 (0.816)
Siblings				
Male	23	7.84 (1.95)	21	6.80 (1.46)
Female	12	6.28 (1.27)	11	4.35 (0.82)
Offsprings				
Male	14	7.19 (1.46)	12	6.99 (1.05)
Female	4	6.53 (1.26)	6	4.55 (0.97)
Overall	58	7.22 (1.75)	58	5.91 (1.63)

DISCUSSION

In this study, we found that the prevalence of hyperuricemia in families of gout patients was 60.3%. This result is higher compared with a previous study[15] conducted at our institution that also involved families of gout patients, which found a prevalence of 26.6%. Compared with the same study, serum uric acid level of the family members of gout patients in this study was lower (8.5 vs. 7.4 mg/dL, respectively).

The importance of genetic factors in hyperuricemia has long been known. The fact is especially evident in studies involving populations that are genetically isolated, such as indigenous peoples.[16] A study in Taiwan found that the hyperuricemia rate in adolescent was higher in indigenous tribes with high gout prevalence (57.7%) compared with non-indigenous population (48.2%) or indigenous tribes with low gout prevalence (34.0%).[17] In this study, genetic defects causing disturbance in uric acid metabolism may explain the higher prevalence of hyperuricemia in families of gout patients. Moreover, obesity and hypertension, which are the known risk factors for hyperuricemia, are also influenced by genetic factors.[18]

As has been stated, hyperuricemia occurs under the influence of internal as well as external factors and this may explain why hyperuricemia was also found in the family members of non-gout patients. Diet is an important external factor that also contributes to the result of our study. Families who live together in one house usually have similar diet. If genetic defects causing disturbance in purine metabolism are already present in the family, regular consumption of high-purine diet could further aggravate the problem.

In this study, a statistically significant prevalence of hyperuricemia and serum uric acid level was observed among families of patients with gouty arthritis; however, it is important to mention several limitations that might influence the result of this study. This was a cross-sectional study and thus we only measured serum uric acid at a given point in time, while the level of serum uric acid in the body may actually fluctuate over period of hours, and transient hyperuricemia sometimes occur in healthy individuals.[19] Also, not all family members gave consent to participate in this study and this might cause bias in the result. A more definitive result could be drawn from further, more detailed studies with better control over both the internal and external factors.

CONCLUSION

The prevalence of hyperuricemia and mean serum uric acid level was significantly higher in families of gout patients compared with families of non-gout patients among Balinese people in this study.

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