

Clinical Characteristics of and Relationship Between Metabolic Components and Renal Function Among Patients with Early-onset Juvenile Tophaceous Gout

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ABSTRACT. Objective. Age of onset of gout has recently decreased; however, patients with early-onset gout remain uncommon, and relevant information is scant. We hypothesized that these patients might exhibit differences in serum urates and other comorbidities compared with adult-onset patients.

Methods. Early-onset gout patients (i.e., juveniles) with (n = 40) and without tophi (n = 47) were enrolled for study. Their clinical characteristics were compared with those of 353 patients with middle-age-onset tophaceous gout and 64 age-matched healthy participants.

Results. Early-onset gout patients with tophi exhibited significantly higher body mass indices and serum urate levels and lower estimated glomerular filtration rates (eGFR) than did those without tophi. Early-onset gout patients with or without tophi demonstrated significantly abnormal lipid profiles and impaired liver or renal function compared with healthy patients. Serum urate levels and gout duration were identified as the principal determinants of tophi development. The presence of tophi might be crucial in decreasing eGFR, which is inversely related to tophi duration or gout duration. Unexpectedly, the most common site of initial gout attacks in early-onset tophaceous gout patients was the ankle, not the toe, which was the most common site in middle-age-onset tophaceous gout patients. The most common site of first tophi occurrence in early-onset patients was a finger, not a toe, which was the most common site in middle-age-onset patients.

Conclusion. Early-onset tophaceous gout patients are more likely to exhibit comorbidities and renal dysfunction than middle-age-onset patients and exhibit distinct first sites of gout attack and tophi occurrence patterns. (J Rheumatol First Release Aug 1 2014; doi:10.3899/jrheum.131240)

Key Indexing Terms:

GOUT HYPERURICEMIA TOPHI COMORBIDITY RENAL DYSFUNCTION

Gouty arthritis is an inflammatory disease caused by uncontrolled hyperuricemia. Suboptimal management of hyperuricemia may contribute to frequent gout attacks and tophi development¹. Gout patients exhibit a remarkably higher prevalence and more components of metabolic syndrome (MetS) than controls do^{2,3,4}. In addition, gout or elevated serum urate levels could independently increase the risk of nonalcoholic fatty liver disease (NAFLD)⁵ and incident kidney disease^{6,7,8}.

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A gout patient presenting with tophi often exhibits a substantially higher serum urate level and more advanced illness⁹ than a patient lacking tophi. Hyperuricemia and the presence of subcutaneous tophi were reported to increase the risk of mortality in patients with gout, and are typically attributed to cardiovascular causes¹⁰.

Although gout has become increasingly prevalent and its onset has shifted to early ages in recent decades^{1,11,12}, it remains uncommon before the age of 20 years, and is referred to as the early-onset of gout in juveniles. The clinical characteristics of early-onset gout were reported to be distinct from those of middle-age-onset gout regarding overweight and family history¹³.

To date, limited data are available for characterizing the early-onset of tophaceous gout in juvenile patients because the condition is not highly prevalent. Whether the critical organ consequences of the disease observed in adult-onset gout patients affect young gout patients remains unclear. We evaluated the hypothesis that patients with early-onset gout, particularly those with tophi, present distinct characteristics and comorbidities compared with those of adult-onset patients.

MATERIALS AND METHODS

From January 2009 to June 2013, we recruited and conducted face-to-face interviews with gout patients in a medical rheumatologic center. All cases fulfilled the 1997 American Rheumatism Association criteria for gout¹⁴. Of these patients, 82% visited their family physicians only when they experienced gout attacks; therefore, these patients were never prescribed urate-lowering agents. Further, 18% of the patients visited rheumatologists, but consulted these agents suboptimally or irregularly.

Clinical characteristics, namely the age at first visit, age at gout and tophi onset, gout and tophi duration, the site of first gout attack and first tophi, body mass index (BMI), hypertension, diabetes mellitus (DM), and family history of gout were recorded. Serum biochemistry results were collected, evaluating the levels of serum urate, cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, fasting blood sugar, glutamate oxaloacetate transaminase (GOT), glutamate pyruvate transaminase (GPT), creatinine, and estimated glomerular filtration rates (eGFR).

Biochemistry tests were performed on venous blood samples after an 8–12 h fast. When a patient was taking lipid-lowering agents or diuretics, or when they had an acute gout attack on the first visit, biochemistry tests were conducted on the subsequent visit, which was at least 1 week after discontinuation of the relevant medications.

Gout duration and tophi duration, measured in years, were determined as the time period from gout onset to first visit, and tophi onset to first visit, respectively. An eGFR was calculated based on serum creatinine levels using the Modification of Diet in Renal Disease Study equation¹⁵.

A family history was considered positive for gout if one or more third-degree or closer relatives of the patients were previously diagnosed with gout. Hypertension was defined as systolic blood pressure (BP) \geq 140 mm Hg, diastolic blood pressure \geq 90 mm Hg, or a history of physician-diagnosed hypertension. Type 2 DM was defined as fasting sugar level \geq 126 mg/dl or a history of physician-diagnosed diabetes.

Patients who were undergoing urate-lowering therapy or chronic steroid therapy, and those who could not remember the precise age of onset or the precise site of initial attack were excluded. Thus, 21 patients were excluded. A total of 87 male early-onset gout patients with tophi ($n = 40$) and without tophi ($n = 47$) were enrolled for study. In addition, 353 patients with middle-age-onset gout whose tophi occurred between ages 40 and 60 years were selected as the control group. Of the early-onset gout patients with tophi and without tophi, and those with middle-age-onset gout, 37 (92.5%), 45 (95.7%), and 317 (89.8%), respectively, were of the Taiwanese Han ethnicity. The remaining patients were Taiwanese aboriginal men. The measured variables of excluded patients were not significantly different from those of the enrolled patients. Moreover, 64 age-matched healthy men were selected as the control group. The study was approved by the Institutional Review Board of Taichung Hospital, Taiwan.

All statistical analyses were performed using PASW Statistics, version 19 for Windows 7.0. A 2-sided p value < 0.05 was considered statistically significant. Categorical data were compared by chi-square test and continuous variables by t -test. Pearson linear correlation was used to test the association of eGFR with gout duration and tophi duration. Multiple logistic regression was performed to validate the hypothesis that serum urate levels or disease duration were independent risk factors for tophi development. Multiple linear regression was also used to verify the hypothesis that tophi or disease duration was associated with eGFR. Because the durations may not be normally distributed, we used log-transformed duration [$\log(\text{duration of gout})$] as an independent variable. All significant confounding factors between early-onset juvenile tophaceous and nontophaceous gout patients were used in both regression models.

RESULTS

The ages of the 40 early-onset juvenile gout patients with tophi ranged between 21 and 39 years (mean $28.8 \pm \text{SD } 5.3$ yrs). Their ages at gout onset ranged between 9 and 19 years

(mean 15.7 ± 2.3 yrs). The ages of the 47 early-onset juvenile patients without tophi ranged between 17 and 37 years (mean 27.0 ± 5.1 yrs), and their ages at gout onset ranged between 12 and 20 years (mean 16.8 ± 1.8 yrs). The early-onset juvenile gout patients with tophi had significantly higher BMI, higher serum urate levels and serum creatinine levels, lower eGFR, and a greater prevalence of a positive family history than did those without tophi (Table 1).

Compared with the age-matched healthy controls, both early-onset juvenile gout patients with and those without tophi demonstrated significantly higher BMI, higher serum urate, cholesterol, triglyceride, LDL cholesterol, GOT, GPT, and serum creatinine levels; significantly lower HDL cholesterol; and lower eGFR.

Those in the early-onset group exhibited significantly higher BMI, higher serum urate levels, lower fasting blood sugar and serum creatinine levels, higher eGFR, and a significantly greater prevalence of positive family history, and lower prevalence of DM than those in the middle-age-onset group.

As shown in Figure 1, eGFR was inversely related to tophi duration among the early-onset juvenile tophaceous gout patients ($\beta = -1.840$, $p = 0.005$). The relationships between eGFR and gout duration were significant among the early-onset gout patients with tophi ($\beta = -1.564$, $p = 0.024$), but were nonsignificant among those without tophi ($\beta = -0.876$, $p = 0.121$).

The relationship between the risk factors and tophi development was analyzed using logistic regression models, and serum urate level, age of onset, gout duration, BMI, eGFR, and hypertension served as the independent variables (Table 2). Patients with elevated serum urate levels were at high risk of developing tophi, and the odds ratio was 2.430 (Model 1; $p < 0.0001$). This significance remained after adjustment for gout duration, BMI, eGFR, and hypertension (Model 5; $p < 0.0001$).

Table 3 lists the linear regression models, including eGFR as a dependent variable, and an additional 5 variables as independent covariables: tophi (with or without), age of onset, BMI, hypertension, and duration (i.e., the tophi duration in early-onset patients with tophi and the gout duration in those without tophi). Because of statistical collinearity, serum urate level was not included as a variable in the linear regression model. Tophi was an independent variable of eGFR when adjusting according to the age of onset and BMI (Model 1; $p = 0.002$), and remained significant when adjusted according to the age of onset, BMI, hypertension, and duration (Model 3; $p = 0.019$). The eGFR in patients with tophi were 10.026 ml/min/1.73 m² lower than those in patients without tophi. In addition, tophi or gout duration was a significant independent variable of eGFR (Model 3; $p = 0.001$). The eGFR declined by 1.286 ml/min/1.73 m² per year of tophi or gout duration. Model 4, in which log-transformed duration was used as an

Table 1. Clinical characteristics of early-onset patients with and without tophi, healthy controls, and middle-age-onset patients with tophi.

Variables	With Tophi, n = 40, mean (SD)	Without Tophi, n = 47, mean (SD) p ¹	Healthy Controls, n = 64, mean (SD)			Middle-age-onset Gout with Tophi, n = 353, mean (SD)		
			p ²	p ³	p ⁴			
Age at first visit, yrs	28.8 (5.3)	27.0 (5.1)	0.116	28.2 (3.9)	0.545	0.182	57.5 (7.5)	<0.0001
Age at gout onset, yrs	15.7 (2.3)	16.8 (1.8)	0.013	—	—	—	41.6 (8.2)	<0.0001
Age at tophi onset, yrs	17.9 (1.6)	—	—	—	—	—	49.4 (5.7)	<0.0001
Gout duration, yrs	13.1 (5.4)	10.2 (5.3)	0.014	—	—	—	15.9 (8.5)	0.004
Tophi duration, yrs	10.8 (5.5)	—	—	—	—	—	8.1 (5.8)	0.005
Body mass index, kg/m ²	31.6 (6.0)	29.1 (4.6)	0.034	24.0 (3.7)	<0.0001	<0.0001	26.0 (3.3)	<0.0001
Uric acid, mg/dl	11.5 (1.8)	9.5 (1.4)	<0.0001	6.2 (1.1)	<0.0001	<0.0001	9.5 (1.4)	<0.0001
Cholesterol, mg/dl	219.0 (56.8)	198.7 (42.4)	0.071	179.0 (33.3)	<0.0001	0.008	209.2 (42.8)	0.323
Triglyceride, mg/dl	172.1 (105.3)	157.8 (74.2)	0.470	86.8 (55.0)	<0.0001	<0.0001	206.2 (138.0)	0.141
HDL, mg/dl	43.3 (8.5)	43.3 (10.6)	0.993	49.0 (11.5)	0.010	0.011	45.3 (12.3)	0.349
LDL, mg/dl	136.4 (40.8)	129.1 (38.6)	0.411	107.8 (27.7)	<0.0001	0.001	122.4 (38.7)	0.034
Fasting sugar, mg/dl	91.5 (12.1)	93.4 (12.5)	0.490	88.1 (7.0)	0.124	0.016	101.1 (23.5)	<0.0001
GOT, mg/dl	31.3 (12.6)	32.4 (18.4)	0.760	21.3 (5.2)	<0.0001	<0.0001	34.0 (22.5)	0.457
GPT, mg/dl	47.0 (36.2)	53.1 (39.2)	0.462	26.0 (13.3)	0.001	<0.0001	36.5 (25.7)	0.080
Creatinine, mg/dl	1.05 (0.21)	0.97 (0.15)	0.043	0.86 (0.12)	<0.0001	<0.0001	1.30 (0.58)	<0.0001
eGFR, ml/min/1.73m ²	84.6 (19.2)	97.4 (17.1)	0.003	107.7 (19.0)	<0.0001	0.006	66.6 (23.0)	<0.0001
Family history, n (%) ^a	35 (87.5)	36 (76.6)	0.191	—	—	—	199 (56.4)	<0.0001
Hypertension, n (%) ^a	21 (52.5)	10 (21.3)	0.002	0 (0.0)	<0.0001	<0.0001	197 (55.8)	0.690
DM, n (%) ^a	1 (2.5)	1 (2.1)	0.908	0 (0.0)	0.204	0.241	54 (15.3)	0.027

¹ Comparison between early onset patients with and without tophi; ² comparison between early onset patients with tophi and healthy controls; ³ comparison between early onset patients without tophi and healthy controls; ⁴ comparison between early onset patients with tophi and middle-aged-onset gout with tophi; ^a using chi-square test. HDL: high-density lipoprotein; LDL: low-density lipoprotein; GOT: glutamate oxaloacetate transaminase; GPT: glutamate pyruvate transaminase; eGFR: estimated glomerular filtration rate; DM: diabetes mellitus.

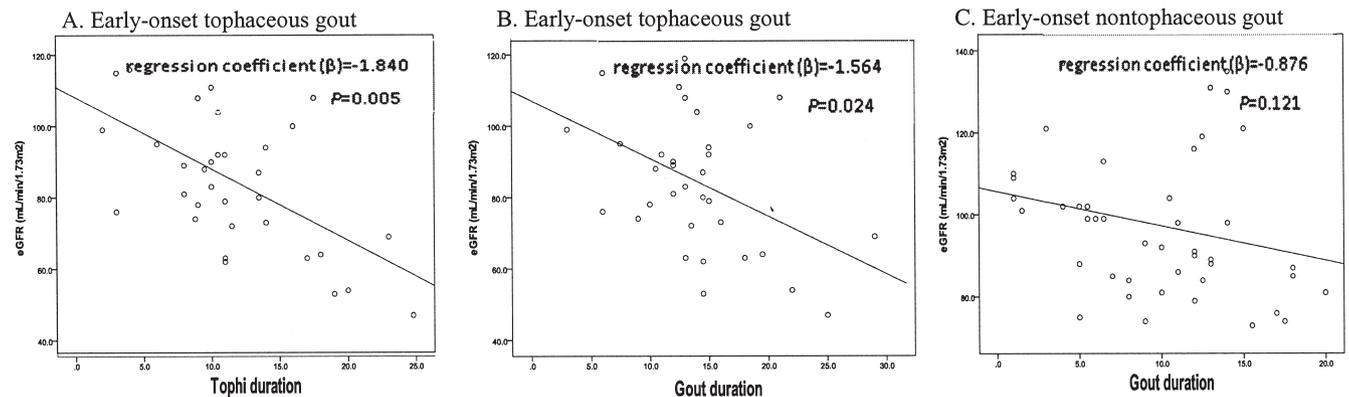


Figure 1. The relationship between estimated glomerular filtration rate (eGFR) and tophi duration (A) or gout duration (B) among patients with early-onset tophaceous gout. The relationship between eGFR and gout duration among patients with early-onset nontophaceous gout (C). All regression coefficients (β) and p values have been adjusted using age of onset, body mass index, and hypertension.

independent variable, yielded results similar to those of Model 3.

Table 4 shows that the most common sites of initial gout attack in early-onset juvenile gout patients with or without tophi were the ankle, followed by the toe. By contrast, the first site of gout attack in middle-age-onset patients was typically a toe, followed by an ankle. In addition, 5 of the 40 early-onset juvenile patients presented the Achilles tendon as the first site of gout attack, whereas none of the 47 early-onset nontophaceous and only 4 of the 353 middle-age-onset tophaceous patients presented a first attack at the Achilles tendon.

As shown in Table 5, the first site of subcutaneous tophi most commonly was a finger among the early-onset juvenile patients, and a toe (primarily the great toe) among the middle-age-onset patients. Further, the rates of occurrence of the first tophi site were significantly different at the Achilles tendon, finger, and elbow between these 2 onset-age groups.

DISCUSSION

Our study demonstrated that patients with early-onset juvenile gout with tophi exhibited higher serum urate levels and more comorbidities than did those without tophi,

Table 2. Multiple logistic regression of the risk factors for early-onset juvenile gout patients with or without tophi. Values expressed as odds ratio (95% confidence interval). The reference group is early-onset patients with tophi versus those without tophi. Model 1, adjusted for age of onset; Model 2, adjusted for age of onset and gout duration; Model 3, adjusted for age of onset, gout duration, and body mass index (BMI); Model 4, adjusted for age of onset, gout duration, BMI, and estimated glomerular filtration rate (eGFR); Model 5, adjusted for age of onset, gout duration, BMI, eGFR, and hypertension.

	Model 1		Model 2		Model 3		Model 4		Model 5	
	OR	p								
Serum urate	2.430	<0.0001	2.811	<0.0001	2.882	<0.0001	2.825	<0.0001	2.880	<0.0001
Age of onset	0.787	0.082	0.879	0.390	0.871	0.364	0.837	0.269	0.822	0.234
Gout duration			1.207	0.008	1.207	0.008	1.173	0.036	1.156	0.064
BMI					0.980	0.732	0.980	0.737	0.934	0.360
eGFR							0.975	0.200	0.976	0.228
Hypertension									2.577	0.224

Table 3. Multiple linear regression analysis of estimated glomerular filtration rate (eGFR) between the early-onset gout patients with or without tophi. Dependent variable: eGFR; Model 1, independent variables: tophi (with or without), age of onset, and body mass index (BMI); Model 2, independent variables: tophi (with or without), age of onset, BMI, and hypertension; Model 3, independent variables: tophi (with or without), age of onset, BMI, hypertension, and duration (tophi duration in patients with tophi and gout duration in those without tophi); Model 4, independent variables: Log-transformed duration instead of original duration presented in Model 3.

	Model 1			Model 2			Model 3			Model 4		
	Coefficient β		p									
	β_u	β_s		β_u	β_s		β_u	β_s		β_u	β_s	
Tophi (with vs without)	-13.824	-0.362	0.002	-10.920	-0.286	0.017	-10.026	-0.263	0.019	-9.750	-0.255	0.025
Age of onset	-0.885	-0.102	0.377	-0.841	-0.097	0.389	-1.137	-0.130	0.218	-1.190	-0.137	0.206
BMI	-0.023	-0.006	0.954	0.413	0.114	0.351	0.119	0.033	0.779	0.191	0.053	0.655
Hypertension				-10.734	-0.274	0.034	-5.839	-0.149	0.236	-8.030	-0.205	0.100
Duration							-1.286 ^a	-0.355	0.001	-8.418 ^b	-0.311	0.004

β_u : unstandardized coefficient, β_s : standardized coefficient. ^aoriginal duration, ^blog-transformed duration.

Table 4. Comparison of sites of first gout attack.

Site	Early-onset Gout with Tophi, n = 40 (%)	Early-onset Gout without Tophi, n = 47 (%)	Middle-Age-Onset Gout with Tophi, n = 353 (%)	p ¹	p ²
Toe	13 (32.5)	16 (34.0)	125 (35.4)	0.879	0.715
Midfoot	3 (7.5)	2 (4.3)	48 (13.6)	0.517	0.277
Ankle	15 (37.5)	24 (51.1)	117 (33.1)	0.205	0.580
Achilles	5 (12.5)	0 (0.0)	4 (1.1)	0.013	<0.0001
Knee	1 (2.5)	4 (8.5)	41 (11.6)	0.230	0.077
Finger	2 (5.0)	0 (0.0)	9 (2.5)	0.121	0.373
Wrist	0 (0.0)	0 (0.0)	5 (1.4)	—	0.449
Elbow	1 (2.5)	1 (2.1)	4 (1.1)	0.908	0.465

Chi-square tests used to determine level of statistical significance. ¹Comparison between early-onset gout patients with and without tophi. ²Comparison between early-onset and middle-age-onset tophaceous gout patients.

age-matched healthy controls, or middle-age-onset tophaceous gout patients. In addition, early-onset tophaceous gout patients presented distinct attack sites compared with middle-age-onset patients.

We determined that serum urate level was the critical determinant of tophi development, and that gout duration was the second most vital determinant. This finding

suggested that hyperuricemia with gout duration played a role in the development of tophi. This concurred with the findings of Nakayama, et al indicating that serum urate levels were the principal factor in tophaceous deposits and that the development of such deposits correlated with both the degree and duration of hyperuricemia⁹.

The BMI were significantly higher among the

Table 5. Comparison of sites of first tophi.

Site	Early-onset Tophaceous Gout, n = 40 (%)	Middle-age-onset Tophaceous Gout, n = 353 (%)	p
Toe	12 (30.0)	132 (37.4)	0.358
Midfoot	6 (15.0)	27 (7.6)	0.112
Ankle	4 (10.0)	69 (19.5)	0.141
Achilles	3 (7.5)	7 (2.0)	0.036
Knee	1 (2.5)	16 (4.5)	0.549
Finger	13 (32.5)	34 (9.6)	<0.0001
Wrist	0 (0.0)	11 (3.1)	0.257
Arm	0 (0.0)	1 (0.3)	0.736
Elbow	1 (2.5)	56 (15.9)	0.023

Chi-square tests used to determine level of statistical significance.

early-onset juvenile gout patients than among the healthy age-matched patients. Further, the BMI values of the early-onset patients with tophi were significantly higher than those of the non-tophi patients. A community-based cohort study consistently indicated that obesity in early life was associated with the incidence of gout in men¹⁶. A Taiwanese study with a large database and data from 1983 to 1999 reported that early-onset gout patients had higher BMI than did middle-age-onset gout patients (27.4 vs 26.0, respectively)¹¹. Compared with patients in that study, our patients exhibited higher BMI in the early-onset juvenile gout groups. A possible cause might be the lifestyle and changes of dietary habits that have occurred in recent decades in Taiwan.

The percentage of hypertension was higher among the early-onset patients with tophi than among those without tophi, suggesting that tophi (or hyperuricemia) are correlated with hypertension. A metaanalysis of 18 prospective cohort studies reported that the future risk of incident hypertension was pronounced among young patients with hyperuricemia¹⁷. In the longitudinal observations of a community-based study, elevated serum urate levels during childhood were associated with increased BP levels that persisted into adolescence¹⁸. The mechanisms of serum urate in the development of hypertension remain unclear. Corry, *et al* reported a possible mechanism where serum urate stimulates the vascular renin-angiotensin system, causing proliferation, angiotensin II production, and oxidative stress in vascular smooth-muscle cells¹⁹.

In our present study, both early-onset patient groups demonstrated significantly abnormal lipid profiles compared with those of the age-matched controls. Among these components, triglyceride levels were particularly distinct. A cross-sectional study indicated that gout was significantly and consistently more prevalent in patients with hypertriglyceridemia and abdominal obesity than in healthy controls²⁰. Another study revealed that high quartiles of serum urate level were more associated with

abnormal lipid components compared with low serum urate quartiles²¹.

The 3 patient groups in our study had elevated serum GOT and GPT. Previous studies have reported that patients with gout and asymptomatic hyperuricemia were more likely to have NAFLD than those lacking such conditions^{22,23}. The development of NAFLD was strongly related to obesity, DM, dyslipidemia, and hypertension, and was considered a hepatic manifestation of MetS^{24,25}. The current findings suggest that gout or hyperuricemia could be associated with liver-related MetS.

In our study, early-onset gout patients with tophi exhibited significantly decreased renal functions compared with those lacking tophi. The results also demonstrated that the eGFR was inversely related to gout duration among early-onset patients with tophi, but not among those without tophi. Moreover, the presence of tophi was an independent variable of eGFR after adjustment for the age of onset, BMI, hypertension, and duration. In addition, duration was a significant independent variable of eGFR. We suggest that tophi or hyperuricemia, along with tophi duration, plays an essential role in decreasing the eGFR among patients with early-onset tophaceous gout.

In contrast to the middle-age-onset patients, the patients in both early-onset gout groups most commonly experienced the first gout attack at the ankle, followed by the toe. Regarding the first tophi, the most common site was a finger among the early-onset tophaceous gout patients, in contrast to a toe among the middle-age-onset patients. Notably, a finger or the Achilles tendon was the more common tophi site among the early-onset tophaceous gout patients than among the middle-age-onset tophaceous gout patients, and the elbow was a less common tophi site among the early-onset group than among the middle-age-onset group. The mechanisms of this difference remain uncertain and warrant further investigation.

Multiple genetic and clinical factors have been reported for identifying high risks of developing gout²⁶. The 869 T/C polymorphism in the *TGF-B* gene was found to be associated with the occurrence of tophi in patients with gout²⁷. Additional research focusing on the relationships among genetic or clinical factors and tophi is required, and a large number of early-onset patients should be sampled.

Our study has 3 limitations. First, because of the low prevalence of this condition, the sample sizes of early-onset patients with tophaceous and nontophaceous gout were 40 and 47, respectively. Second, although the biochemistry data were obtained at least 1 week after discontinuing the use of diuretics, the duration of diuretic use before visiting the clinic was not recorded. Third, not all patients were diagnosed using liver ultrasonography; thus, the patients were analyzed using only serum liver enzymes (GOT and GPT).

Patients with early-onset gout may not be aware of hyperuricemia or the future risks associated with the

condition; however, they may consult rheumatologists when subcutaneous tophi appear. Thus, the current findings yield crucial implications, suggesting that early-onset gout patients who develop tophi must be examined because of the high risk of potential comorbidities.

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