

# Seasonality of Gout in Korea: A Multicenter Study

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Received: 25 July 2014

Accepted: 10 October 2014

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The object of this study was to evaluate the seasonality of gout in Korea. We retrospectively examined data from 330 patients seen at nine rheumatology clinics, treated with urate lowering therapy (ULT) more than one year after stopping prophylactic medication. Demographic data, clinical and laboratory features, and seasonality of gout onset and flares were collected. Season was classified in three-month intervals. The mean age was 52.2 yr and mean disease duration was 26.8 months. The male to female count was 318:12. The onset of acute gouty attacks was obtained in 256 patients. Gout developed most commonly in summer season (36.7%) ( $P < 0.001$ ) and in June (15.6%,  $P = 0.002$ ). During ULT, there were 147 (male 97.3%) gout flares. Although there was no statistically significant difference, gout flares were more common in summer (30.6%). Aggravating factors were identified in 57 flares: alcohol (72.0%) was most common. In the patients who attained target serum uric acid ( $< 6$  mg/dL) at the end of prophylaxis, gout flares were high in fall (35.8%) and September (17.0%). In Korea, the summer is most common season of gout onset and there is a tendency for gout flares to increase during ULT in summer/fall season.

**Keywords:** Gout Onset; Flares; Seasonality; Summer; Korea

## INTRODUCTION

Gouty arthritis is inflammatory arthritis, and has seasonal variation that differs widely by geographic area (1-5). Acute gouty flares are more common in the spring in the USA (1) and Italy (2), in the autumn in Australia (3), spring and summer in Israel (4) and summer in the UK study (5). The reasons for dominant seasonality in different countries are not clear. There are suggestions of increased physical activity contributing to the effect (1, 5). Serum uric acid/lipid/cortisol levels and changes in diet, alcohol consumption, temperature, or infection are suggested (6).

There were seasonal variations of non-communicable disease such as chronic obstructive pulmonary disease, gastritis, falls and injuries in India (7). Although factors associated with gout are frequent and excessive alcohol consumption, high body mass index/blood pressure/total cholesterol/uric acid and proteinuria in Korea (8), the seasonality or causes of gouty arthritis have not been reported. Therefore we conducted this study to explore gout onset and flares in Korea.

## MATERIALS AND METHODS

We retrospectively examined data from 330 patients seen at nine rheumatology clinics between January and June 2013. Potential study subjects were those seen at the rheumatology clinic with gouty arthritis, taking urate lowering agents, with urate lowering therapy (ULT) more than one year after stopping prophylactic medications. Patients were excluded if they had adrenal insufficiency, other rheumatic diseases such as osteoarthritis, or had irregular follow ups after starting ULT. The diagnosis of gouty arthritis depends on finding monosodium urate crystal by polarization microscope or American College of Rheumatology (ACR) classification criteria (9). Demographic and clinical data were collected by chart review. Disease duration was defined from the onset of

first gout attack to the time of starting ULT. Gout is defined by 1) physician diagnosis, or by 2) any three out of four criteria of patient-reported features (gout flare, joint pain at rest, swollen joint, warm joint) (10). The onset date of acute gouty attacks was obtained. Flares during the period from stopping prophylaxis to one year later were counted. Season was classified by three-month time intervals (the period from March 1 through May 31 was defined as spring). All 4 seasons were analyzed in patients records collected during January and June 2013.

### Statistical analysis

Season and month of gout onset and flares were tested by a goodness of fit test. Statistical analysis used SPSS ver. 19 (SPSS, Inc., an IBM Company, Chicago, IL, USA). Null hypotheses of no difference were rejected if *P* values were less than 0.05.

### Ethics statements

The institutional review board at each hospital approved this study (GCIRB2014-207 Gachon University Gil Hospital; 2013-044 NHIS Ilsan Hospital; 2-1409-044 Inje University Ilsan Paik Hospital; 13-083 Ajou University School of Medicine; 2014177-1373 Chung Ang University Hospital; 14-056 Inha University Hospital; 14103-002 Korea University Ansan Hospital; 2014-08-022-001 Ewha Womans University Medical Center; 06-2012-209, SNU Boramae Medical Center). The board waived informed consent requirements.

## RESULTS

### Characteristics of patients

Three hundred and thirty patients were enrolled. The mean age was 52.2 yr, the mean disease duration was 26.8 months, and

**Table 1.** Demographic and baseline characteristics

Parameters (n = 330)	Findings
Age (yr, mean ± SD) at the starting ULT	52.2 ± 13.8
Sex (male:female)	318:12
Body mass index (kg/m <sup>2</sup> )	25.6 ± 2.9
Disease duration (months)	26.8 ± 60.7
Comorbidity (No., %)	
Hypertension	139 (42.1)
Diabetes mellitus	56 (17.0)
Hyperlipidemia	109 (33.0)
Cardiovascular diseases	27 (8.2)
Kidney disease	44 (13.3)
Presence of tophi (No., %)	22 (6.7)
At onset time of gout	
Serum uric acid (mg/dL)	8.1 ± 2.0
CCr (mL/min/1.73 m <sup>2</sup> )	78.2 ± 30.6
Glucose (mg/dL)	112.4 ± 36.0
Total cholesterol (mg/dL)	195.0 ± 77.7
Triglyceride (mg/dL)	225.3 ± 141.2
High-density lipoprotein (mg/dL)	39.7 ± 8.7

ULT, urate lowering therapy; NSAIDs, non-steroidal anti-inflammatory drugs; CCr, calculated creatinine.

the mean body mass index was 25.6. The male to female count was 318:12. Comorbidities included hypertension (42.1%), diabetes mellitus (17.0%), hyperlipidemia (33.0%), cardiovascular diseases (8.2%), and kidney diseases (13.3%). Tophus was present in 6.7% (Table 1).

### Seasons of gout onset and flares

The onset time of acute gouty attacks was obtained in 256 patients. The most common season of gout onset was summer (36.7%, *P* < 0.001), followed by spring (25.4%), fall (20.7%), and winter (17.2%) (Table 2). June was most common month of gout onset (15.6%, *P* = 0.002) (Table 3).

In our study there were one hundred forty-seven episodes (male 97.3%) of gout flares. During ULT, 113 of the 330 patients (34.2%) experienced at least one gouty attack in the period from stopping prophylaxis to one year later. Summer was most common season for gout flares (30.6%), then fall (25.2%), spring (22.4%), and winter (21.8%), although without a statistically significant difference (Table 4, Fig. 1A). Twenty flares (13.6%) happened in June, followed by August (10.2%), September (9.5%) and February (9.5%, Fig. 1B). Aggravating factors were identified in 57 flares: alcohol (72.0%), concomitant drugs (14.0%),

**Table 2.** Seasonality of gout onset

Gender	No. (%)	Spring	Summer	Fall	Winter	<i>P</i> value*
Total	256	65 (25.4)	94 (36.7)	53 (20.7)	44 (17.2)	< 0.001
Males	246 (96.1)	62 (25.2)	92 (37.4)	51 (20.7)	41 (16.7)	< 0.001
Females	10 (3.9)	3 (30.0)	2 (20.0)	2 (20.0)	3 (30.0)	0.940

\*By Goodness of fit test.

**Table 3.** Monthly distribution of gout onset

Month (n = 256)	No. (%) of 256
January	9 (3.5)
February	19 (7.4)
March	24 (9.4)
April	21 (8.2)
May	20 (7.8)
June	40 (15.6)
July	27 (10.5)
August	25 (9.8)
September	18 (7.0)
October	20 (7.8)
November	17 (6.6)
December	16 (6.3)

*P* = 0.002, by Goodness of fit test.

**Table 4.** Seasonality of gout flares in the patients with urate lowering therapy after prophylaxis ended

Gender	No. (%)	Spring	Summer	Fall	Winter	<i>P</i> value*
Total	147	33 (22.4)	45 (30.6)	37 (25.2)	32 (21.8)	0.415
Males	143 (97.3)	33 (23.1)	43 (30.1)	37 (25.9)	30 (21.0)	0.449
Females	4 (2.7)	0	2 (50.0)	0	2 (50.0)	> 0.999

\*By Goodness of fit test.

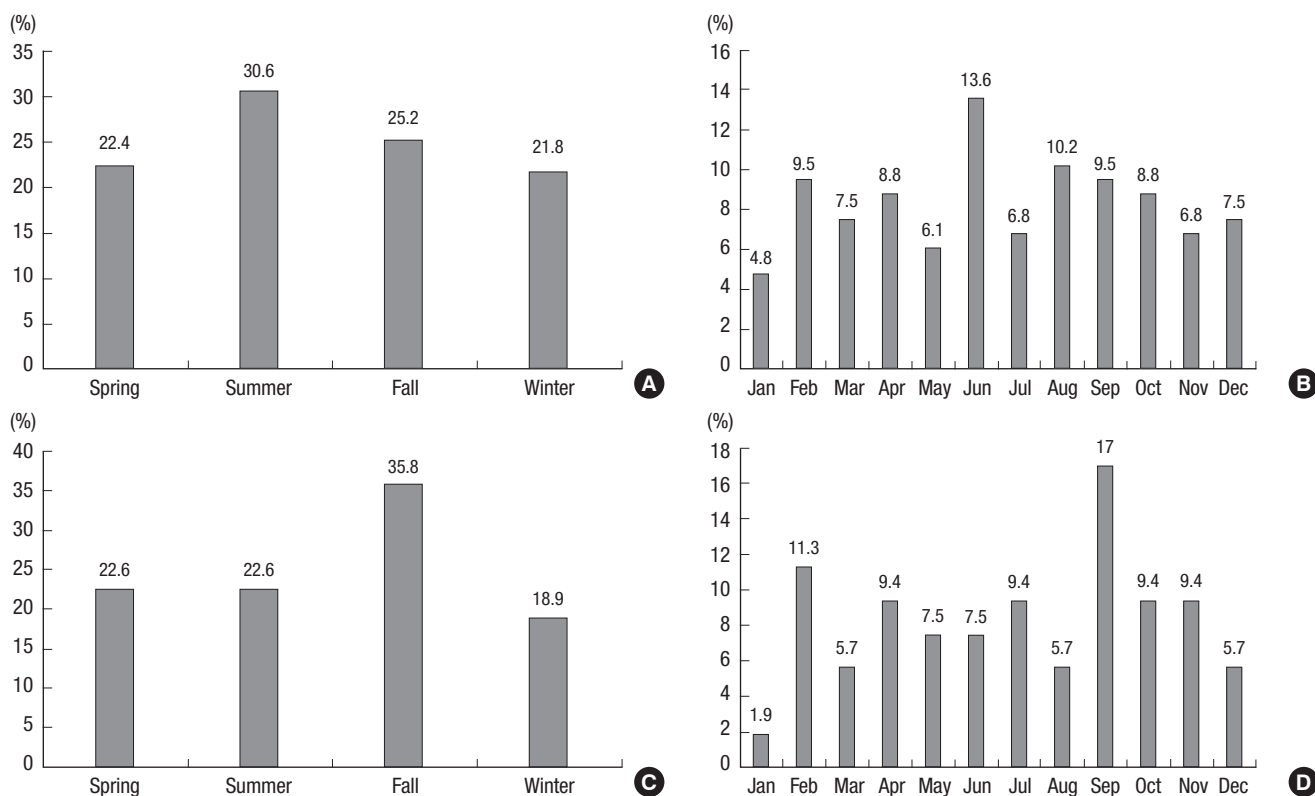


Fig. 1. The seasons and months of gout flares. Those in all episodes (A, B) and in patients who attained target serum uric acid at the end of prophylaxis (C, D).

food (10.5%), and work/exercise (8.8%). The proportion of patients reporting alcohol use in summer was higher (88.9%) than other seasons (data not shown). For subanalysis, we evaluated gout flare in the patients who attained target serum uric acid (SUA) level ( $< 6$  mg/dL) at the end of prophylaxis ( $n = 139$ ). Fifty-three episodes occurred. Gout flares were highest in fall ( $n = 19$ , 35.8%, Fig. 1C), and September ( $n = 9$ , 17.0%, Fig. 1D). Aggravating factors were identified in 20 flares (alcohol,  $n = 11$ , 55.0%, data not shown).

## DISCUSSION

In this study, we investigated the seasonality of gout onset and flares during ULT in Korea. Summer was most common season of gout onset, similar result as reported in other countries (4, 5). This summer dominant seasonality disappeared in patients with gout flares during ULT. A retrospective study in UK (5) found that gout increased from late April to mid-September (the summer period). The reason for the increased gout attack risk during summer was unclear, but they suggested environmental factors such as temperature, dehydration, or increased physical activity. In our study, summer or fall from June to November had the highest gout attack. Although we have no specific data, we hypothesized that increased activity during these periods resulting in minor trauma and increased temperatures result-

ing in dehydration could influence gout attacks in our study. We also suggest that weather could affect gout onset, but other factors such as diet, drug withdrawal may affect gout flares during ULT.

Seasonality in gout attacks varies across geographic differences. Arber et al. (4) reported in Israel more attacks of gout in the spring and summer, and statistically significantly increased attacks in July. Reports from Australia (3) found elevated risk in autumn, hypothesizing that the onset of cold weather precipitated recurrent attacks of gout. Spring was consistently a common acute gout season in the studies from North America (1, 11), and from Italy (2, 12). The definitions of spring (Mar 22-Jun 21) in those studies (1, 12) were slightly different from our study. In our cohort, the most common month of gout onset and flares during ULT was June, which was categorized into summer. In the north-eastern Italy study (2), they categorized spring into three month periods like our study, but spring was April through June. They also reported the fewest gout attacks were during October (fall). There was a spring peak of occurrence of acute gout and a fall/winter peak for pseudogout in Slovakia (13). Punzi et al. (12) reported the lowest gout attacks occurred in summer (Jun 22-Sep 21), quite different from our result.

We found the lowest risk of acute gouty attacks of onset in winter as in previous results (1, 4, 5). We also noted lowest risk of gout flares during ULT in the winter, although not statistically

significant. Lower temperature seems not to be associated with more gout flares by precipitating monosodium urate crystals as previously reported (14, 15). The reasons for such seasonal variations are unknown, but changes in the patient's diet, alcohol consumption, physical activity, and changes in temperature, humidity, and barometric pressure may play a role (1, 6, 14-16). Lee et al. (8) reported that excessive and frequent consumption of alcohol was associated with increased risk of gout in Korea. In our study, patients with gout flares had higher alcohol consumption in summer (n = 16/41, 39.0%, data not shown).

SUAs, which are highest in the summer (17), or uric acid elevation by heat stress (18) may be related to our results. There are seasonal variations in cortisol level (19, 20). The lowest cortisol levels in healthy persons were found during the spring and summer, while the highest levels were during fall and winter (19). Patients with gout have increased levels of low-density lipoprotein cholesterol/triglyceride, and decreased levels of high density lipoprotein cholesterol compared with healthy controls (6, 21, 22). Unfortunately we did not have any data about cortisol level, and have just small serum uric acid or lipid profile, so we could not include these factors in our analyses.

There are some limitations in our study. First, it was a retrospective study and the ethnicity is limited to Koreans. Second, since our study sample was small and from a tertiary hospital, there is a possibility of selection bias. Third, since we had no information about changes in diet, and only limited laboratory data at gout flares, it is hard to examine the relationship between diet, SUA or lipid level and gout flares. Large prospective studies are needed to clarify risks for gout onset/flares and the effects of seasonal variation.

We have several important strong points in our study. First, we have data from multicenter rheumatology clinics, and selected compliant patients who had been examined regularly for more than one year, allowing us to assess flares over four seasons, and second, it is the first report about gout seasonality in Korea.

In conclusion, summer is most common season of gout onset in Korea although the seasonal effect is lower for patients taking ULT.

## DISCLOSURE

The authors have no conflicts of interest to disclose.

## AUTHOR CONTRIBUTION

HJC contributed to the design of the study, performed the analysis, interpreted the results and wrote the manuscript. HJB contributed to the design of the study, interpretation of the results and approval of final version of the manuscript. JBJ contributed to the idea of gout seasonality. All authors except JBJ contribut-

ed to the patients enrolled and data collected. The manuscript has been seen and approved by all the authors. Study concepts & design: Choi HJ, Baek HJ, Jun JB. Data collection: Choi HJ, Lee CH, Lee JH, Yoon BY, Kim HA, Suh CH, Choi ST, Song JS, Joo HY, Choi SJ, Lee JS, Shin KC, Baek HJ. Analysis and interpretation of results, writing: Choi HJ, Baek HJ. Final approval: all authors.

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