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# Presence of tophi is a predictive factor of arterial stiffness in patients with gout

WooSeong Jeong[1] · Seung-Jae Joo[2] · Jinsoek Kim[1] · Jae-Geun Lee[2] · Joon Hyouk Choi[2]

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## Abstract

The objective of this study is to determine whether the presence of tophi could predict an increase in arterial stiffness. Between June 2017 and June 2018, the augmentation index (AI) was measured using SphygmoCor® for patients with gout who visited the Jeju National University Hospital in South Korea. Patients were divided into the following groups: group with tophi and group without tophi. Medical records, laboratory data, and AI were retrospectively analyzed. One hundred and twenty patients with gout or participated in the study, with most (96.7%) of the patients being male. The mean duration of the disease was 7.0 years. At the time of the examination, 99 patients (82.5%) were treated with a uric acid-lowering agent. Of the total patients, 24 (19.7%) had tophi. Patients with tophi were significantly older (60.2 ± 11.6 years vs. 53.8 ± 13.0 years, $p = 0.031$), had longer disease duration (13.0 ± 6.5 years vs 5.5 ± 5.4 years, $p < 0.001$), and higher AI@75 (28.7 ± 7.8 vs 20.9 ± 10.0, $p = 0.001$) than those without tophi. In the multiple linear regression analysis, tophi was shown to be a significant predictor of high AI ($p = 0.040$). The presence of tophi is a predictor of increased arterial stiffness in patients with gout. Therefore, more strict control of cardiovascular disease risk factors is needed in the treatment of patients with tophi.

**Keywords** Gout · Uric acid · Arterial stiffness

## Introduction

Gout is the most common form of inflammatory arthritis caused by the deposition of monosodium urate crystals in and around joints, and it is often associated with hyperuricemia [1]. The prevalence of gout has been reported to be 1–4% in North America and Western Europe, and is increasing in more affluent countries in recent decades [2]. Many studies have reported that gout and hyperuricemia are associated with increased all-cause mortality and cardiovascular mortality [3–8]. Clarson et al. have shown through meta-analysis that there is a significant association between gout and mortality from cardiovascular disease (CVD) or coronary heart disease (CHD) [9]. Increased arterial stiffness is an independent predictor of CVD [10–12]. Many studies have shown a significant correlation between uric acid levels and arterial stiffness [13–16]. Persistent hyperuricemia can cause increase in arterial stiffness which consequently affects cardiovascular morbidity and mortality. Thus, we thought that tophi formed by long-lasting gout can be a predictor of increased arterial stiffness in patients with gout [17]. The central aortic pressure is composed of an initial incident pressure caused by contraction of left ventricle and reflected pressure from the periphery (Fig. 1). As arterial stiffness increases, the velocity of incident waves and reflected waves increases. If the reflected wave arrives early to the central aorta, the central aortic systolic blood pressure (SBP) will rise. This increased pressure is called augment pressure [18]. AI is an indirect measure of arterial stiffness, and it represents the percentage of the augmentation pressure (AP) for the pulse pressure (PP) [10]. Therefore, the present study aimed to determine whether the presence of tophi could predict arterial stiffness in patients with gout by measuring the AI.

✉ Joon Hyouk Choi
valgom@hanmail.net

[1] Division of Rheumatology, Department of Internal Medicine, Jeju National University Hospital, Jeju National University School of Medicine, Jeju, South Korea

[2] Division of Cardiology, Department of Internal Medicine, Jeju National University Hospital, Jeju National University School of Medicine, Aran 13gil (Ara-1-dong), Jeju-Si, Jeju 63241, South Korea

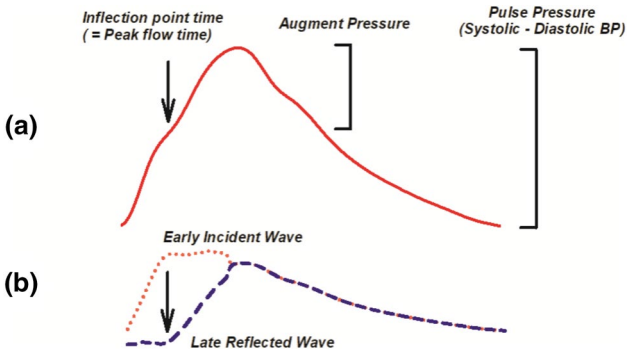


**Fig. 1** The central pulse wave is formed by the addition of the late reflection wave from the periphery to the initial incident wave caused by the contraction of the left ventricle. **a** Central aortic pressure. **b** Reconstructed constituent forward and backward waves

## Materials and methods

This hospital-based observational study was approved by the ethical committee of the institutional review board of Jeju National University Hospital, and all participants provided informed and written consent.

### Study design and patient selection

Patients with gout, who visited our center between June 2017 and June 2018, were enrolled. Individuals who met the American College of Rheumatology gout criteria were considered to be patients with gout. Patients underwent standardized medical history taking and examinations, anthropometric measurements, and laboratory tests. Patients with abnormal heart rhythms and those who had an operator index of less than 80 were excluded from this study. The participants were divided into the following groups according to the presence of tophi: those with tophi and those without tophi.

### Clinical evaluation

The patient clinical records were retrospectively reviewed, and additional history taking, physical examinations, and blood tests were performed to obtain the following data: age, sex, body mass index (BMI), previous treatment of gout, other comorbidities [diabetes mellitus (DM), hypertension (HT), hyperlipidemia, chronic kidney disease (CKD), and CVD], and laboratory findings.

### Treatment

All patients were prescribed allopurinol or febuxostat to lower uric acid levels. Colchicine, prednisolone (PD), and non-steroidal anti-inflammatory drugs (NSAIDs) were prescribed for acute gout attack and prophylaxis.

### Arterial stiffness evaluation

Brachial blood pressure (BP) measurements and the AI were assessed in the sitting position after 10 min of rest. Brachial BP was measured before the AI by using a digital sphygmomanometer (Omron® M6, Omron Corporation, Kyoto, Japan). We analyzed the waveforms of each patient's central aortic pressure using SphygmoCor® (AtCor, Sydney, Australia) after applanation of the left radial artery and recording the central aortic pressure estimate. The AI assessed using SphygmoCor® provided data for central systolic BP (SBP), diastolic BP (DBP), mean BP, and central pulse pressure, as well as AP, AI, and AIx@75 (expressed as the AI corrected for a heart rate of 75 beats/min). The SphygmoCor® uses an average method to obtain a representative central blood pressure. Therefore, 10–12 waves are analyzed. The operator index is an indicator of the accuracy and consistency of AI measurements. SphygmoCor®'s successful AI measure criteria are operator index of over 80.

### Statistical analysis

Data are presented as mean ± standard deviation for continuous variables or as frequency for categorical variables. The significance of differences among groups was determined using the *t* test and Chi-squared test. Linear regression analysis was performed to evaluate whether the presence of tophi could predict vascular stiffness. Furthermore, a multivariate linear regression analysis was performed to exclude the effects of age, total cholesterol, creatinine, BMI, disease duration, HT, hyperlipidemia, DM, NSAID frequency, gout attack frequency, and CV. All statistical analyses were performed using SPSS 20 (version for Windows; SPSS Inc., Chicago, IL, USA). A $p$ value $< 0.05$ was considered statistically significant.

## Results

### Baseline clinical characteristics

The study enrolled 124 patients. Of these patients, 2 with an operator index of less than 80 and 2 with arrhythmia were excluded. Thus, 120 patients were finally included in the study. The mean patient age was 55.1 ± 12.9 years, and 116 (96.7%) patients were male. The mean BMI was 26.3 ± 2.9 kg/m$^2$, indicating that most patients were overweight. The mean uric acid and creatinine levels were 5.9

and 1.2 mg/dL. Concomitant diseases were HT (44.2%), DM (8.3%), CKD (19.2%), CVD (6.7%), and hyperlipidemia (33.3%). Histories of drinking alcohol and smoking were noted in 38 (31.7%) and 74 (60.0%) patients, respectively. Uric acid-lowering drugs were used in 99 (82.5%) patients. Febuxostat was used in 91 (75.8%) patients, and allopurinol was used in 5 (4.2%) patients. The mean disease duration was 7.0 years, and the mean treatment duration was 28.2 months. Thirty-six (30.0%) patients received treatment for less than 3 months. Twenty-one patients (17.5%) were diagnosed with gout at the time of enrollment and had not received uric acid-lowering treatment. Of the total patients, 24 (19.7%) had tophi. On comparing patients with tophi and those without tophi, it was found that patients with tophi were older (60.2 years vs. 53.8 years, $p=0.031$), had a longer uric acid-lowering treatment duration (44.7 months vs. 24.1 months, $p=0.041$), and had a longer disease duration (13.0 years vs. 5.5 years, $p<0.001$). There are significantly more patients who received uric acid-lowering treatment in the group with tophi than in the group without tophi (100% vs. 78.1%, $p=0.007$). The duration of uric acid-lowering treatment (44.7 months vs. 24.1 months, $p=0.041$) was significantly longer in patients with tophi than in those without tophi. There were more CKD (33.3% vs. 15.3%, $p=0.049$) patients and higher creatinine (1.3 mg/dL vs. 1.2 mg/dL, $p=0.048$) levels in the group with Tophi. The sex ratio, BMI, smoking rate, and drinking rate were not different between the two groups. There were no significant differences in the liver function test results, lipid profile, and C-reactive protein level between the two groups (Table 1), but the uric acid (5.6 mg/dL vs. 5.9 mg/dL, $p=0.407$) and total cholesterol (179.2 mg/dL vs. 182.8 mg/dL, $p=0.669$) levels were lower in patients with tophi than in those without tophi. There was no statistically significant difference in the proportion of patients who had gout attack between the groups (64.3% vs. 50.0%, $p=0.197$). The frequency of gout attack that occurred during the last year was 1.43 and 0.88 ($p=0.106$) in the groups with and without tophi, respectively. The proportion of patients who received PD for gout attack was higher in patients with tophi (10.2% vs. 20.8%, $p=0.172$), and the proportion of patients receiving NSAIDs was significantly higher in patients without tophi (54.1% vs. 29.2%, $p=0.029$). The frequency of taking PD (0.20 vs. 0.25, $p=0.761$) and taking NSAIDs (1.22 vs. 0.63, $p=0.082$) for gout attack was not different between the patients with and without tophi.

**Table 1** Baseline characteristics according to the study group

| | No tophi ($N=96$) | Tophi ($N=24$) | $p$ |
|---|---|---|---|
| Age | 53.8 ± 13.0 | 60.2 ± 11.6 | 0.031 |
| Sex, male | 92 (95.8) | 24 (100.0) | 0.583 |
| BMI | 26.4 ± 3.0 | 25.6 ± 2.3 | 0.208 |
| Comorbidities | | | |
| HT | 39 (40.6) | 14 (58.3) | 0.118 |
| DM | 8 (8.3) | 2 (8.3) | 1.000 |
| CKD | 15 (15.3) | 8 (33.3) | 0.049 |
| CVD | 6 (6.2) | 2 (8.3) | 0.660 |
| Hyperlipidemia | 31 (32.3) | 9 (37.5) | 0.628 |
| Alcohol | 54 (56.8) | 18 (75.0) | 0.104 |
| Smoking | 30 (31.2) | 8 (33.3) | 0.844 |
| Disease duration (year) | 13.0 ± 6.5 | 5.5 ± 5.4 | < 0.001 |
| ULT | 75 (78.1) | 24 (100) | 0.007 |
| ULT duration (month) | 24.1 ± 29.9 | 44.7 ± 44.9 | 0.041 |
| Febuxostat | 67 (69.8) | 24 (100.0) | 0.002 |
| Allopurinol | 5 (5.2) | 0 (0.0) | 0.582 |
| Statin | 31 (32.3) | 9 (37.5) | 0.628 |
| Attack | 62 (64.6) | 12 (50.0) | 0.189 |
| Attack frequency (year) | 1.45 ± 1.6 | 0.88 ± 1.1 | 0.096 |
| Anti-inflammatory drug | | | |
| PD | 10 (10.4) | 5 (20.8) | 0.168 |
| PD frequency | 0.21 ± 0.69 | 0.25 ± 0.53 | 0.784 |
| NSAID | 52 (54.2) | 7 (29.2) | 0.028 |
| NSAID frequency | 1.24 ± 1.59 | 0.63 ± 1.13 | 0.077 |
| Cr | 1.2 ± 0.2 | 1.3 ± 0.4 | 0.048 |
| Uric acid | 5.9 ± 1.7 | 5.6 ± 2.3 | 0.407 |
| Total cholesterol | 182.8 ± 31.5 | 179.2 ± 40.5 | 0.669 |
| LDL | 108.2 ± 29.9 | 99.3 ± 33.7 | 0.268 |
| HDL | 46.3 ± 11.8 | 48.7 ± 13.4 | 0.428 |
| TG | 181.0 ± 153.3 | 153.3 ± 102.7 | 0.447 |
| CRP | 0.13 ± 0.10 | 0.14 ± 0.10 | 0.754 |

Data are expressed as mean ± standard deviation or number (percentage), $p<0.05$ considered significant

*BMI* body mass index, *HT* hypertension, *DM* diabetes mellitus, *CKD* chronic kidney disease, *CVD* cardiovascular disease (including stroke and myocardial infarction), *ULT* uric acid-lowering treatment, *PD* prednisolone, *NSAID* non-steroidal anti-inflammatory drug, *Cr* creatinine, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *TG* triglyceride, *CRP* C-reactive protein

## Augmentation index

Peripheral SBP and DBP as well as pulse pressure were not different between patients with tophi and those without tophi, but central SBP was significantly higher in patients with tophi than in those without tophi. Patients with tophi had a significantly higher AP (13.8 mmHg vs. 9.3 mmHg, $p=0.006$), AI (28.3% vs. 21.4%, $p=0.012$), and AIx@75 (28.7% vs. 20.9%, $p=0.001$) when compared with the findings in those without tophi (Table 2). Figure 2 shows the distribution of AIx@75 in patients with or without tophi. On analyzing AIx@75 according to tertiles, we found that

**Table 2** Analysis of augmentation index according to the study group

| | No tophi ($N=98$) | Tophi ($N=24$) | $p$ |
|---|---|---|---|
| Peripheral systolic BP (mmHg) | 133.3 ± 15.6 | 137.0 ± 17.7 | 0.303 |
| Peripheral diastolic BP (mmHg) | 78.9 ± 11.3 | 82.3 ± 11.6 | 0.196 |
| Peripheral pulse pressure (mmHg) | 54.5 ± 11.6 | 54.3 ± 12.0 | 0.950 |
| Central systolic BP (mmHg) | 120.4 ± 14.9 | 132.0 ± 23.4 | 0.027 |
| Central diastolic BP (mmHg) | 80.2 ± 11.5 | 83.8 ± 11.8 | 0.172 |
| Central pulse pressure (mmHg) | 39.8 ± 10.7 | 48.2 ± 23.4 | 0.100 |
| Augmentation pressure (mmHg) | 9.3 ± 6.8 | 13.8 ± 8.2 | 0.006 |
| Augmentation index (%) | 21.4 ± 12.4 | 28.3 ± 9.5 | 0.012 |
| Augmentation index@75 (%) | 20.9 ± 10.0 | 28.7 ± 7.8 | 0.001 |

Data are expressed as mean ± standard deviation, $p<0.05$ considered significant

*BP* blood pressure

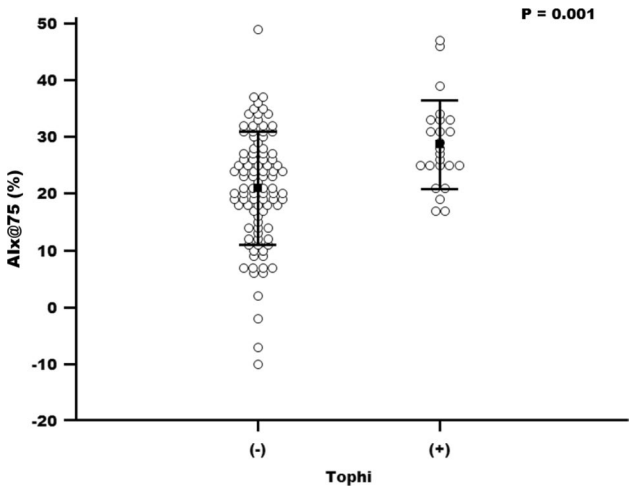


**Fig. 2** Distribution of AIx@75 according to the presence of tophi (AIx@75: augmentation index 75). AIx@75 is significantly higher in the group with tophi ($p=0.001$)

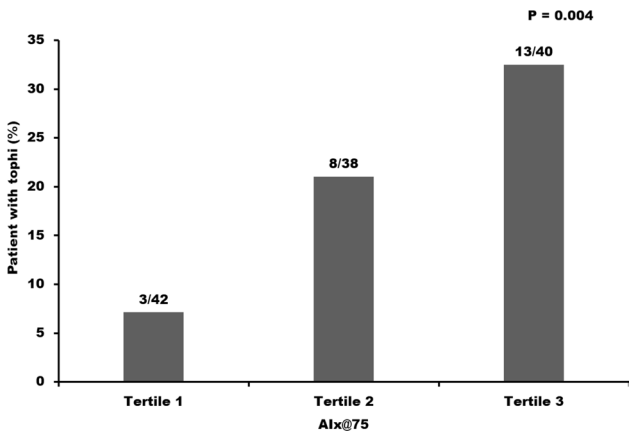


**Fig. 3** AIx@75 and number of patients with tophi ($p=0.004$) (AIx@75: augmentation index 75). AIx@75, − 10 to 19, 20–26, and 27–49 in tertiles 1, 2, and 3, respectively

the number of patients with tophi increased significantly as the AIx@75 increased ($p=0.004$) (Fig. 3).

Univariate linear regression analysis found that the presence of tophi was a significant predictor of a high AIx@75 ($p=0.001$). In the multivariate linear regression analysis, which showed an increasing trend in the AIx@75, the presence of tophi remained a significant predictor of a high AIx@75 ($p=0.040$) (Table 3).

## Discussion

Tophi are deposits of urate crystals in joints and surrounding tissues, usually occurring after an average of more than 10 years of acute gout attack [19]. The rate of formation of tophi and the occurrence of gout are proportional to the degree and duration of hyperuricemia [20]. This study demonstrated that the presence of tophi could predict increased vascular stiffness in patients with gout. The mean AI for the average age of patients with tophi (60.2 years) and patients without tophi (53.8 years) calculated by the formula provided by SphygmoCor® manufacturer AtCor Medical are 26.2% and 21.4%. In our study, AIx@75 (28.7% vs. 20.9%, $p=0.001$) was significantly higher in the group with tophi than the group without tophi and higher than the average of predicted AI in the general population. The disease duration was significantly longer in those with tophi than in those without tophi. This is a predictable result, because longer durations of gout are associated with a greater chance of tophi occurrence. Age was significantly higher in patients with tophi and was a significant contributor to increased AIx@75, and it might have been associated with the higher AIx@75 in this patient group. However, the multivariate analysis showed that AIx@75 was significantly higher in patients with tophi than in those without tophi after adjusting for age and other variables. An increase in AIx@75 was associated with an increase in the number of patients with

**Table 3** Linear regression analysis of tophi and augmentation index for the prediction of increased vascular stiffness

| | Unadjusted B-coefficient (95% CI) | *p* value | Adjusted B-coefficient (95% CI) | *p* value |
|---|---|---|---|---|
| Age | 0.346 (0.219–0.473) | < 0.001 | 0.257 (0.083–0.431) | 0.004 |
| Tophi | 7.688 (3.345–12.030) | 0.001 | 5.256 (0.253–10.260) | 0.040 |
| Hyperlipidemia | 4.550 (0.768–8.332) | 0.019 | 1.143 (− 2.868 to 5.153) | 0.573 |
| Cr | 7.431 (1.026–13.836) | 0.023 | 4.140 (− 3.716 to 11.997) | 0.298 |
| Total cholesterol | − 0.067 (− 0.127 to − 0.007) | 0.030 | − 0.061 (− 0.120–0.002) | 0.042 |
| BMI | − 0.679 (− 1.298 to − 0.059) | 0.032 | − 0.520 (− 1.176 to 0.136) | 0.119 |
| Disease duration | 0.256 (− 0.028 to 0.539) | 0.077 | 0.146 (− 0.195 to 0.487) | 0.398 |
| Gout attack frequency | − 1.059 (− 2.259 to 0.141) | 0.083 | − 1.339 (− 4.199 to 1.522) | 0.355 |
| HT | 3.197 (− 0.431 to 6.826) | 0.084 | − 3.928 (− 8.410 to 0.553) | 0.085 |
| NSAIDs frequency | − 1.039 (− 2.227 to 0.148) | 0.086 | 0.573 (− 2.257 to 3.403) | 0.688 |
| CVD | 6.277 (10.950–13.503) | 0.088 | 3.041 (− 4.096 to 10.178) | 0.399 |
| DM | 4.782 (− 1.764 to 11.328) | 0.151 | − 1.336 (− 8.660 to 5.989) | 0.718 |
| Smoking | 2.209 (− 1.694 to 6.112) | 0.265 | | |
| CKD | 2.481 (− 2.134 to 7.095) | 0.289 | | |
| PD | 1.924 (− 3.584 to 7.431) | 0.449 | | |
| Allopurinol | 2.800 (− 6.319 to 11.919) | 0.544 | | |
| CRP | 5.434 (− 12.912 to 23.718) | 0.559 | | |
| Alcohol | − 1.087 (− 4.847 to 2.673) | 0.568 | | |
| ULT | − 1.221 (− 6.019 to 3.577) | 0.615 | | |
| Gender | − 2.569 (− 12.726 to 7.588) | 0.617 | | |
| NSAID | − 0.783 (− 4.431 to 2.865) | 0.672 | | |
| Febuxostat | − 0.865 (− 5.125 to 3.396) | 0.688 | | |
| Uric acid | − 0.047 (− 1.037 to 0.943) | 0.925 | | |
| ULT duration | − 0.022 (− 0.055 to 0.052) | 0.952 | | |
| PD frequency | 0.011 (− 2.752 to 2.774) | 0.994 | | |

*Cr* creatinine, *BMI* body mass index, *HT* hypertension, *NSAID* non-steroidal anti-inflammatory drug, *CVD* cardiovascular disease (including stroke and myocardial infarction), *DM* diabetes mellitus, *CKD* chronic kidney disease, *PD* prednisolone, *CRP* C-reactive protein, *ULT* uric acid-lowering treatment

tophi (Fig. 3). This result indicates that tophi and AIx@75 are closely related. Thus, the presence of tophi is considered to be an independent predictor of increased vascular stiffness.

There was no significant difference in peripheral SBP between patients with tophi and those without tophi, and the difference between peripheral SBP and central SBP was significantly smaller in patients with tophi than in those without tophi (9.2 mmHg vs. 12.9 mmHg, $p = 0.030$). This is because the central SBP of patients with tophi was higher than that of patients without tophi (132.0 vs. 120.4, $p = 0.027$). Several studies have shown that an increase in central SBP is associated with the occurrence of CVD [21, 22]. Perez-Ruiz et al. showed that the presence of tophi was associated with a high CVD risk [23]. In our study, central SBP was higher in patients with tophi than in those without tophi, and this result supports the findings of the study by Perez-Ruiz et al.

Many studies have reported that arterial stiffness is increased by inflammation [23]. Inflammation also occurs during gout attacks, which may affect arterial stiffness. However, the frequency of gout attacks was not correlated with AIx@75 in this study. This may be due to the fact that inflammation caused by gout attack does not persist for a long time and is improved shortly by medication; thus, inflammation does not significantly affect arterial stiffness. There was no difference in CRP levels between patients with and without tophi in this study.

Unlike previous studies, this study showed that the uric acid level and disease duration were not associated with increased vascular stiffness. This might be associated with the fact that most patients were treated with uric acid-lowering agents, and their uric acid levels remained low at the time of AI measurement.

Total cholesterol levels were lower in patients with tophi, probably because more patients received treatment for hyperlipidemia. AIx@75 was higher in patients with tophi, although total cholesterol levels were lower in this patient group. Therefore, it is thought that the condition associated with tophi formation has a greater influence on vascular stiffness than the effect of improving vascular stiffness with

hyperlipidemia treatment. The data regarding AIx@75 suggested that patients with lower total cholesterol levels might have a higher AIx@75. This is probably associated with the fact that a higher proportion of patients received lipid-lowering treatment among patients with a high AIx@75 than patients with a low AIx@75(42.6% vs. 23.7%, $p=0.028$). Moreover, the total cholesterol level was actually lower in patients with a high AIx@75 than patients with a low AIx@75 (173.9 mg/dL vs. 190.4 mg/dL, $p=0.012$).

Increased vascular stiffness is closely related to the occurrence of CVD. Therefore, if it can be predicted, the occurrence of CVD can be prevented. In this study, we confirmed that the presence of tophi was a predictor of increased vascular stiffness in patients with gout. In patients with tophaceous gout, the risk of CVD is high; thus, very strict risk modification is needed. It might be helpful to start treatment a little earlier than the recommendation of current guidelines to prevent tophi formation in patients with gout.

Few studies have reported that uric acid-lowering treatment reduces vascular stiffness in CKD patients [24]. However, it is still unclear whether the decrease in vascular stiffness by uric acid-lowering treatment can reduce the incidence of CVD and thereby reduce cardiovascular mortality. Therefore, it is necessary to investigate the initial treatment timing, the cut-off value of vascular stiffness, and the new target treatment level of uric acid to prevent an increase in vascular stiffness and prevent the occurrence of CVD.

The present study has several limitations. First, this study compared the AIx@75 values among patients with gout. Therefore, the AIx@75 values obtained in this study may not be the same for the normal healthy group. Second, the use of steroids is a risk factor for arterial stiffness. However, we could only provide data on the frequency with which steroids were used, and there were limited data on the duration and dosage of the steroids. However, most patients do not have prolonged use of steroids or NSAIDs when they have gout attacks, because they show rapid improvement. Therefore, the use of steroids in this study did not seem to have a significant effect on arterial stiffness. Third, we included patients who had already been treated with uric acid-lowering agents at the time of enrollment; thus, data on the disease duration and uric acid-lowering treatment duration might not have been accurate. Fourth, if we could have analyzed the differences between patients taking allopurinol and those taking febuxostat, it would have been more beneficial in our data and analysis. However, most of the patients in our study were taking febuxostat and there was a limitation of the analysis. In Korea, febuxostat is mainly used to treat gout. Because many Koreans have the *HLA-B*5801* allele associated with allopurinol hypersensitivity [25]. Fifth, there was a difference in age between patients with tophi and those without tophi. However, the presence of tophi could predict an increase in vascular stiffness even after excluding the influence of age. In collinearity statistics, all variance inflation factors were less than 10, and multicollinearity was not observed. Finally, most patients were treated with febuxostat; thus, we could not compare the effects of different types of uric acid-lowering drugs.

Although the present study had limitations, the study might indicate that actual clinical data can be obtained by analyzing patients who have already been treated or who have been newly diagnosed with gout.

In conclusion, the presence of tophi is an independent predictor of increased vascular stiffness in patients with gout. Therefore, very strict control of CVD risk factors is needed in the treatment of patients with tophi. Moreover, efforts should be made to prevent the development of tophi in patients with gout. Thus, future studies investigating the target uric acid level are necessary to prevent the occurrence of CVD.

**Author contributions** Conceptualization: WSJ and JHC. Data curation: WSJ. Formal analysis: WSJ, JHC, and JGL. Investigation: WSJ and JHC. Methodology: WSJ and JHC. Resources: JHC. Supervision: JHC, SJJ, and JSK. Writing—original draft: WSJ. Writing—review and editing: WSJ, JHC, SJJ, and JSK.

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## Compliance with ethical standards

**Conflict of interest** WooSeong Jeong, Seung-Jae Joo, Jinsoek Kim, Jae-Geun Lee, and Joon Hyouk Choi declare that they have no conflict of interest.

**Ethical standards** This hospital-based observational study was approved by the ethical committee of the institutional review board of Jeju National University Hospital, and all participants provided informed and written consent.

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