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Gout as a risk factor for osteoporosis
A Korean population-based study

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Abstract

Uric acid acts as both an antioxidant and a pre-oxidant that induces oxidative stress; thus, it plays a paradoxical role in inflammation. However, the effect of gout, a hallmark of hyperuricemia, on osteoporosis remains unclear. Therefore, this study aimed to investigate the association between gout and osteoporosis. This retrospective cohort study used data from the Korean National Health Insurance Service Database. In total, 628,565 participants who were diagnosed with gout and prescribed medications for gout for at least 90 days were selected. The control cohort included patients with no history of gout or use of gout medication. Age and sex 1:1 propensity score matching and Cox proportional hazards models were used to investigate risk factors for osteoporosis. In total, 305,810 patients with gout met the inclusion criteria. Compared with the control group, both men and women with gout showed an increased incidence rate ratio of osteoporosis. In the stratified analysis by age, patients with gout showed an increased incidence rate ratio for osteoporosis in all age groups, except for those over 80 years of age (P < .001). Gout showed an increased hazard ratio of 1.48 (95% CI: 1.45–1.51, P < .001). The female sex has also been identified as a risk factor for osteoporosis. Patients in their 70s had the highest HR. Gout is significantly associated with the risk of osteoporosis. In particular, the results of this study showed that the incidence of osteoporosis increased up to four times in male patients in their 20s with gout compared to without gout.

Abbreviations: BMD = bone mineral density, HR = hazard ratio, ICD-10 = International Classification of Diseases-10, NHIS = National Health Insurance Service, IRR = incidence rate ratio.

Keywords: gout, osteoporosis, population-based study, uric acid

1. Introduction

Osteoporosis is a progressive systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures.[1,2] Several interacting factors, including clinical, medical, behavioral, nutritional, and genetic factors, contribute to the risk of osteoporosis.[3] Aging and female menopause are the dominant risk factors for osteoporosis.[4] Low body weight, low body fat percentage, and low body mass index (BMI) increase the risk of low bone mass and rapid bone loss.[5–8] Several medical conditions, including gastrointestinal diseases, hematologic disorders, and hypogonadal states[9] are associated with secondary osteoporosis. Glucocorticoids, which are commonly used to treat rheumatic diseases, are representative agents that affect bone mineral density (BMD).[10]

Gout is a chronic inflammatory disease that is characterized by hyperuricemia. Uric acid can act as both an antioxidant and a pre-oxidant, inducing oxidative stress related to inflammation.[11] Inflammatory cytokines have been shown to stimulate osteoclast bone resorption.[11] Previous studies on the effects of gout on osteoporosis due to the paradoxical function of uric acid have shown conflicting results.[12–15] In other words, gout was reported to increase the risk of osteoporosis[12,13] in several studies, whereas it was reported that there was no association of fracture risk associated with osteoporosis in other studies.[14,15]

This population-based study aimed to investigate the association between gout and osteoporosis using the Korean National Health Insurance Service (NHIS) database.

2. Methods

2.1. Database and study population

In this retrospective cohort study, we used data from the Korean NHIS database. The NHIS was launched in 2000 as a single

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insurer and covers the entire Korean population by integrating 375 insurance associations. The NHIS comprises the eligibility database, National Health Screening Database, basic demographic variables (e.g., age, sex, residential area, and type of health insurance), International Classification of Diseases-10 (ICD-10) disease codes, healthcare utilization (diagnosis, length of stay, treatment costs, and services received), and prescription records (drug code, days prescribed, and daily dosage). This study was approved by the Institutional Review Board of the Chungbuk National University Hospital (CBNUH IRB approval no. 2020-08-007). Patient consent was not required as the study was based on secondary data released for research purposes.

2.2. Study cohort selection and osteoporosis assessment

Data from the NHIS database covering the period from 2002 to 2019 were used in this study. Data from 2002 were excluded as a washout period for new patient extraction, and data from 2018 and 2019 were also excluded to ensure a follow-up period of of at least two years. In total, 628,565 participants diagnosed with gout (ICD-10, M10) and prescribed medications for gout, such as colchicine, allopurinol, febuxostat, and benzbromarone, for at least 90 days, were selected from the NHIS database. In this study, the ICD code for gout diagnosis was matched with the gout-specific medication code to improve its reliability of gout diagnosis. As this study used diagnostic and medication prescription codes, laboratory findings including uric acid levels could not be confirmed.

Patients with osteoporosis were assigned a diagnosis code for osteoporosis with or without pathological fractures (ICD-10 codes M80 and M81, respectively). Comorbidities were considered potential confounding factors. Comorbidities included hypertension (I10-I15), diabetes (E10-E14), dyslipidemia (E78), ischemic heart disease (I20-I25), and stroke (I63-I64) and were defined by the ICD-code.

In this study, 215,711 patients with cancer, 85,331 patients with end-stage renal disease, and 21,713 patients with osteoporosis were excluded. A total of 305,810 new patients with gout were identified. The control cohort included patients who had never had a gout diagnostic code, or had never been administered any gout medication. Age and sex 1:1 propensity score matching was performed for the selected control cohort. A flowchart of the study cohort selection process is shown in Figure 1. We also performed a subgroup analysis according to the age group (<65 or ≥65 years) based on the age of 65 years, the standard for elderly and non-elderly groups, and sex.

2.3. Statistical analyses

The baseline demographic and clinical characteristics of patients with gout and controls were analyzed using the chi-square test or Student's t test. The Cox proportional hazards model was used to evaluate the effect of gout on the risk of osteoporosis, and the results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs); we used different adjustment models for potential confounders. There was no multicollinearity between the variables and the proportional hazard assumption was met. The cumulative osteoporosis incidence was determined using the Kaplan–Meier method and compared between the two cohorts using the log-rank test. Analyses were performed using the SAS statistical package (version 9.4; SAS Institute Inc., Cary, NC) and R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $P < .05$.

3. Results

The database included the medical information of almost all Korean individuals enrolled in the NHIS database. A total of 628,565 new patients diagnosed with gout were identified
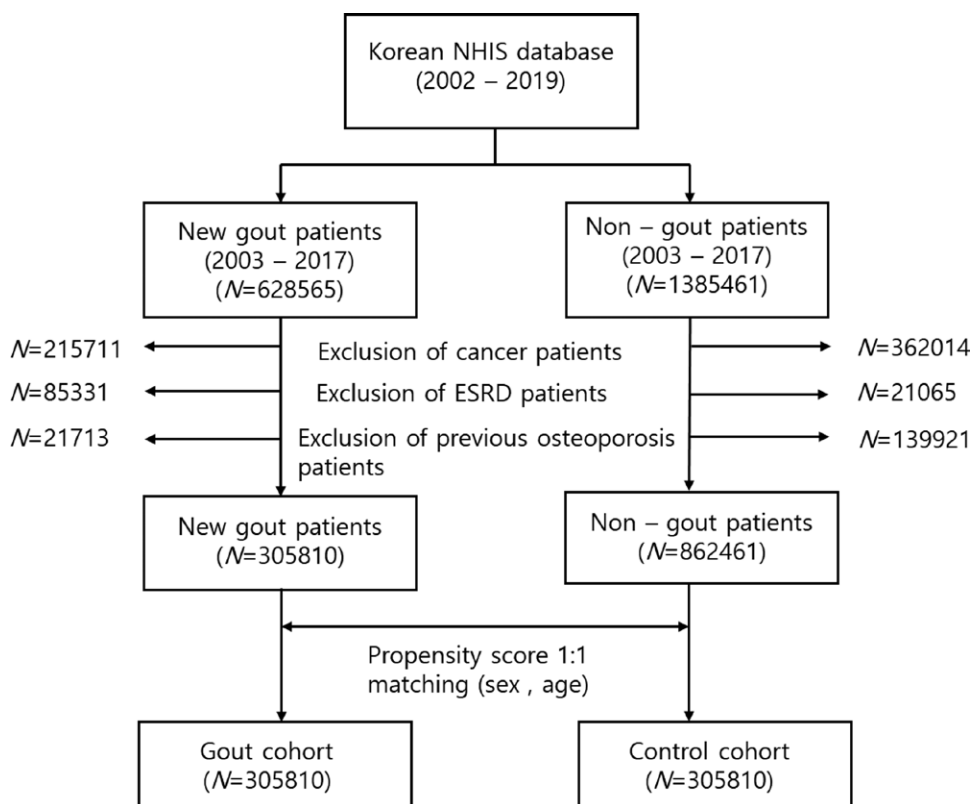

Figure 1. Flowchart of the selection of the study population from the National Health Insurance Service database. In total, 305,810 patients with gout and 305,810 control participants were compared via propensity score matching.

during the 18-year period between 2002 and 2019. Ultimately, 305,810 patients with gout met our inclusion criteria. The demographic and clinical characteristics of the study cohort at the baseline are shown in Table 1. This analysis revealed that gout was most prevalent in the 40 to 49 years age group. Only 3.62% of patients with gout were women. No significant differences were observed in the mean age and sex distribution between patients with gout and controls, indicating that the groups were well-matched. The percentage of comorbidities, including hypertension, diabetes, dyslipidemia, ischemic heart disease, and stroke, was significantly higher in the gout patient group than that in the control group ($P < .001$, Table 1).

The incidence rate of osteoporosis in patients with gout compared with that in the control group is shown in Table 2. A total of 25,357 patients with gout and 19,030 controls developed osteoporosis during the study period. The overall incidence rate of osteoporosis (per 1000 person-years) significantly increased in patients with gout (10.6 in the gout group vs 7.95 in the control group). The incidence rate ratio (IRR) was 1.33 (95% CI: 1.31–1.36). Stratified analysis by sex and age revealed differences between groups (Table 2). Compared with the control group, both male (IRR 1.38; 95% CI: 1.35–1.40) and female patients (IRR 1.21; 95% CI: 1.16–1.27) with gout showed an increased IRR of osteoporosis. In addition, patients with gout showed an increased IRR for osteoporosis in all age groups, except for those over 80 years of age ($P < .001$, Table 2).

The Cox proportional hazards model was used to investigate risk factors for osteoporosis (Table 3). In the analysis, gout showed an increased HR of 1.48 (95% CI: 1.45–1.51; $P < .001$) after adjustment for multivariable Cox proportional hazards regression. Female sex was also a risk factor for osteoporosis (HR: 4.49; 95% CI: 4.38–4.61; $P < .001$). A significant association between osteoporosis and age was observed. HR was the highest in the 70- to 79-year age group (HR: 20.93; 95% CI: 19.55–22.41, $P < .001$). In contrast, in the 30- to 39-year age group, the HR was 1.26 (95% CI: 1.17–1.35, $P < .001$), which was relatively low; however, it was significant. All comorbidities included in this study showed inverse results (Table 2): hypertension, HR = 0.88 (95% CI: 0.86–0.91, $P < .001$); diabetes, HR = 0.93 (95% CI: 0.91–0.95, $P < .001$); dyslipidemia, HR = 0.76 (95% CI: 0.74–0.78, $P < .001$); ischemic heart disease, HR = 0.95 (95% CI: 0.93–0.97, $P = .001$); and stroke HR = 0.95 (95% CI: 0.92–0.97, $P < .001$).

We analyzed the cumulative incidence by dividing the patients into age groups (based on age 65, <65, or ≥65 years) and sex. Figure 2 shows that the cumulative incidence of gout increased compared to that in the control group in both the <65 and ≥65 years groups during the follow-up period. The cumulative incidence of patients with gout was higher than that of the control group in both male (Fig. 3B) and female groups (Fig. 3A). In particular, the difference markedly increased in female patients with gout despite the relatively small number of participants (Fig. 3A).

4. Discussion

In this study, we analyzed the incidence rate and risk of osteoporosis in patients with gout compared with those in participants without gout using medical data from 2002 to 2019. The incidence rate and HR for osteoporosis were higher in the gout group. When participants were divided into subgroups, the cumulative incidence was more prominent in the <65-year age group than in the ≥65-year age group and the increased in both female and male group.

The global disease burden of osteoporosis is increasing.[16] The epidemiology of osteoporosis in Asians appears to be relatively unknown, in contrast to Western societies. Asia is reported to have a high incidence and burden of osteoporotic hip fractures, and this region is expected to account for 37% of all hip fractures by 2025.[17] According to a study published in 2014, the prevalence of osteoporosis in Korea was 7.3% in men and 38.0% in women aged ≥50 years, and the prevalence of osteopenia in Korea was 46.5% in men and 48.7% in women aged ≥50 years.[18] Another Korean study reported that the crude prevalence of osteoporosis was 13.1% in men and 24.3% in women, according to WHO criteria, in participants (aged 40–79 years).[19] When femoral neck BMD data from Korea were compared with Chinese, Japanese, and US study data, the mean BMD of male participants in Korea was significantly lower than that of non-Hispanic white, non-Hispanic black, and Mexican American individuals in all age groups ($P ≤ .05$).[19]

Gout is a chronic disease caused by hyperuricemia. Uric acid has been reported to be effective in preventing inflammation owing to its antioxidant function.[11] However, some reports suggest that uric acid is a preoxidant that induces inflammation

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Table 1

Demographics and clinical characteristics of the study cohort.

Variables	Gout patients (N = 305,810)	Controls (N = 303,810)	P value
Sex			
Male	294,750	294,750	
Female	11,060	11,060	
Age (yr)			
<30	30,374	30,374	
30–39	74,654	74,654	
40–49	84,324	84,324	
50–59	67,163	67,163	
60–69	33,692	33,692	
70–79	12,729	12,729	
≥80	2874	2874	
Underlying diseases			
Hypertension	189,997 (62.13%)	122,639 (40.1%)	**<.001**
Diabetes	164,688 (53.85%)	112,435 (36.77%)	**<.001**
Dyslipidemia	261,089 (85.38%)	181,184 (59.25%)	**<.001**
Ischemic heart disease	86,767 (28.37%)	60,569 (19.81%)	**.001**
Stroke	26,458 (8.65%)	20,823 (6.81%)	**<.001**

Values are presented as number of patients (%).

Table 2

Incidence of osteoporosis in patients with gout and in controls, stratified by age and sex.

Variables	Gout (N = 305,810)			Controls (N = 303,810)			
	N, %	PY	IR	N, %	PY	IR	IRR (95% CI)
Overall	25,357	149,778.38	10.6	19,030	117,982.64	7.95	1.33 (1.31–1.36)
Sex							
Male	21,201	131,253.3	9.10	15,461	101,375.87	6.62	1.38 (1.35–1.40)
Female	4156	18,525.08	68.49	3614	16,606.77	56.57	1.21 (1.16–1.27)
Age, yr							
20–29	818	4603.48	3.47	204	1267.22	0.86	4.05 (3.477–4.73)
30–39	2223	13,524.03	3.66	965	6648.28	1.58	2.58 (2.39–2.78)
40–49	4394	28,058.74	6.20	2839	20,239.35	3.40	1.55 (1.48–1.63)
50–59	6624	39,609.04	12.80	5189	33,196.35	10.04	1.28 (1.23–1.32)
60–69	6891	41,151.03	29.53	5937	36,147.75	25.76	1.15 (1.11–1.19)
70–79	3683	19,272.51	48.78	3284	17,299.63	44.40	1.1 (1.05–1.15)
≥80	724	3559.56	53.15	612	3184.07	50.10	1.06 (0.95–1.18)

CI = confidence interval, IR = incidence rate, IRR = incidence rate ratio, PY = 1000 person-years.

Table 3

Cox proportional hazard model of risk factors for osteoporosis.

	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Gout	1.34 (1.31–1.36)	<.001	1.48 (1.45–1.51)	<.001
Female sex	8.57 (8.36–8.79)	<.001	4.49 (4.38–4.61)	<.001
Age				
30–39	1.19 (1.11–1.27)	<.001	1.26 (1.17–1.35)	<.001
40–49	2.28 (2.13–2.43)	<.001	2.51 (2.35–2.68)	<.001
50–59	5.28 (4.96–5.63)	<.001	5.87 (5.501–6.267)	<.001
60–69	13.15 (12.34–14.02)	<.001	14.44 (13.52–15.41)	<.001
70–79	23.23 (21.75–24.81)	<.001	20.93 (19.55–22.41)	<.001
≥80	27.77 (25.601–30.14)	<.001	17.25 (15.85–18.77)	<.001
Hypertension	1.78 (1.74–1.81)	<.001	0.88 (0.86–0.91)	<.001
Diabetes	1.36 (1.33–1.38)	<.001	0.93 (0.91–0.95)	<.001
Dyslipidemia	1.02 (1–1.04)	.05	0.76 (0.74–0.78)	<.001
Ischemic heart disease	1.52 (1.49–1.55)	<.001	0.95 (0.93–0.97)	.0001
Stroke	2.05 (1.98–2.09)	<.001	0.95 (0.92–0.97)	<.001

CI = confidence interval, HR = hazard ratio (using the Cox proportional hazards model).
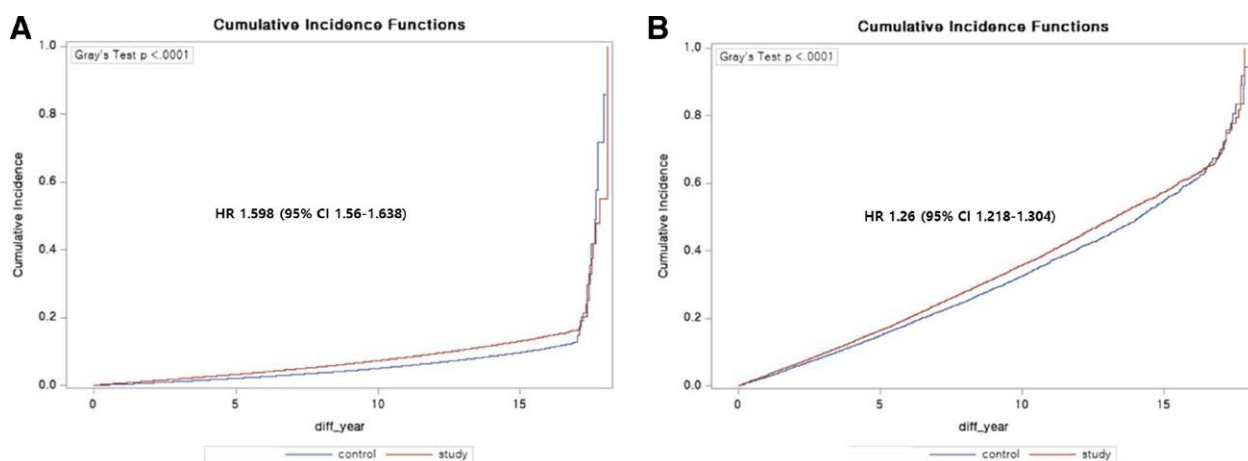

Figure 2. Cumulative incidence of osteoporosis in patients with gout and controls, stratified by age. (A) < 65 years, (B) ≥ 65 years. CI = confidence intervals, HR = hazard ratio.

after metabolism.[11] These differences between the studies were due to the heterogeneous characteristics of gout.

Although there is a possibility of a relationship between rheumatic disease and osteoporosis, few studies have confirmed this association. In addition, previous studies on the association between rheumatic diseases, including rheumatoid arthritis and osteoporosis, were mainly related to the effects of glucocorticoids

on osteoporosis.[20–22] We investigated the incidence and risk of gout, a relatively common inflammatory arthritis among rheumatic diseases in patients with gout. Compared with other rheumatic diseases, gout is not commonly treated with glucocorticoids despite being a chronic inflammatory disease. The association between gout and osteoporosis is not well known, although a few studies have examined this association. These
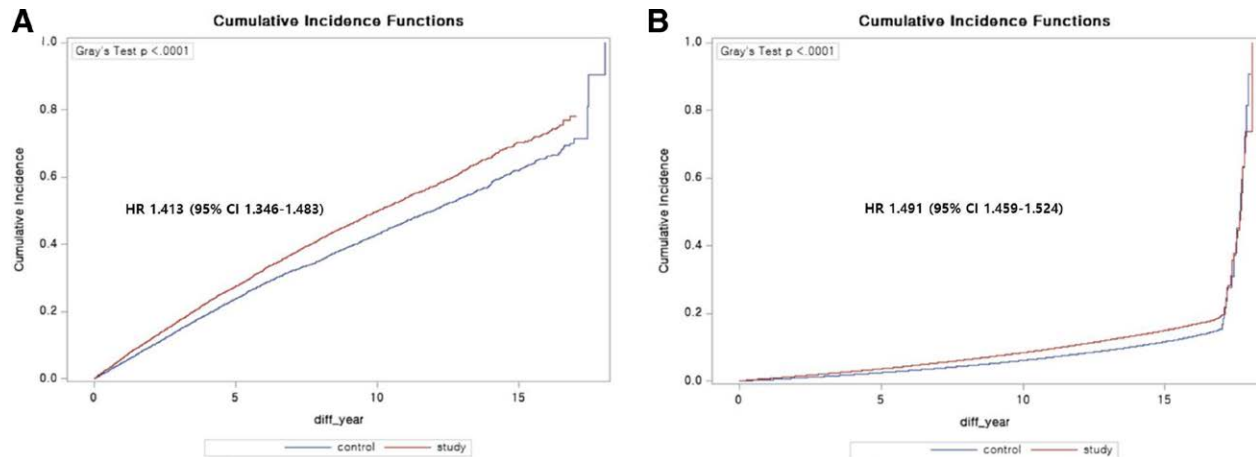
Figure 3. Cumulative incidence of osteoporosis in patients with gout and controls stratified by sex. (A) female group, (B) male group. CI = confidence intervals, HR = hazard ratio.

studies have shown conflicting results due to the paradoxical mechanism of uric acid in oxidative stress. Previous studies that examined the association between serum uric acid concentrations and BMD and considered important potential confounders and risk factors reported that higher levels of serum uric acid are associated with higher BMD values at skeletal sites and a lower prevalence of osteoporosis.[23–27] In contrast, several studies have reported that gout increases the risk of osteoporosis.[12,13] In addition, other studies have reported no association between gout and osteoporosis.[14,15] Several complex factors seem to be at work in these conflicting results. Asians have a relatively lower BMI on average, which also could affect unfavorable results for osteoporosis compared with those of western patients.[14] The risk of osteoporosis may be partly related to the age and sex distribution in the different studies. In addition, gout can show diverse conditions based on the clinical status or composition of the patient group with gout, including uric acid level or disease activity related to chronic inflammation, which can affect the study results. It is possible that these factors may have influenced the results of this study. Further studies are needed to confirm this hypothesis.

Metabolic syndrome is a cluster of abdominal obesity, dyslipidemia, hyperglycemia, and hypertension.[28] Patients with gout are associated with these comorbidities, and their BMI are often high.[29] Therefore, the risk of osteoporosis in these patients is expected to decrease owing to their high BMI. In this study, the risk of osteoporosis was significantly reduced in patients with hypertension, diabetes, and dyslipidemia, which was consistent with our prediction. In contrast, patients with gout showed the opposite results. In our study, gout may have been greatly affected by the mechanism of stimulating osteoclast bone resorption by inducing inflammation rather than by the protective effect of uric acid. Other risk factors (female sex and old age) showed a significant increase in the HRs for osteoporosis, which is consistent with the results of previous studies.[4]

The present study has several strengths. First, this is the first study to analyze the association between gout and osteoporosis by using large-scale Korean insurance data. Gout was defined as a combination of ICD diagnosis code and specific gout medication to increase the reliability of the diagnosis. Finally, the demographic and clinical information of domestic patients with gout were identified, and a sub-analysis was performed according to sex and age. However, this study had several limitations. First, we could not obtain BMD or BMI values of the participants. In addition, the serum uric acid levels of patients with gout could not be obtained because of the limitations of the medical claims data. Additional prospective studies are needed to address these issues.

5. Conclusion

In conclusion, the incidence and risk of osteoporosis was higher in Korean patients with gout. Although the effect is much smaller than that of age and female sex, which are the typical risk factors for osteoporosis, it is true that gout has a significant effect on osteoporosis compared with other common comorbidities, such as hypertension and diabetes constituting metabolic syndrome. In particular, the results of this study showed that the incidence of osteoporosis increased up to four times in younger male patients in their 20s with gout compared to without gout, despite having conditions in which bone density is expected to be the highest. Therefore, when the patients have been diagnosed with gout at a young age, it is recommended to actively screen for osteoporosis.

Author contributions

JHK was responsible for the conception and design, analysis and interpretation, and drafting and revising the manuscript. SRK was responsible for the data acquisition, analysis, and interpretation. GWK was responsible for the data acquisition, analysis, and interpretation. IAC was responsible for conception, design, drafting, and revision of the manuscript. All authors have read and approved the final manuscript.

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