J Rheum Dis J Rheum Dis 2023;30(2):88-98
https://doi.org/10.4078/jrd.2022.0001
pISSN: 2093-940X, eISSN: 2233-4718

Review Article

# Epidemiology and treatment-related concerns of gout and hyperuricemia in Korean

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Gout is the most common form of inflammatory arthritis that affects mainly middle-aged men, and there is clear evidence of an association between hyperuricemia and the risk for gout. Increasing prevalence of gout and hyperuricemia has been reported in many countries. The prevalence of gout and hyperuricemia are constantly increasing in Korea with the patients at risk for developing a variety of comorbidities. Although there have been studies on the association between gout or serum uric acid level and several neurodegenerative diseases, cancer, and cardiovascular mortality, the causal relationship between gout and these comorbidities are still unclear. The associations of substantial economic burden with hyperuricemia, gout attack, and suboptimal treatment are well known. Gout is a disease that requires lifelong management including lifestyle modification. However, gout is poorly managed worldwide although effective urate-lowering drugs exist. In this review, we addressed epidemiological studies and treatment-related problems in the Korean population with gout or hyperuricemia to obtain the best clinical outcomes and reduce their medical burden.

**Keywords:** Gout, Hyperuricemia, Epidemiology, Comorbidity, Treatment

## INTRODUCTION

Gout is the most common form of inflammatory arthritis that affects mainly middle-aged men, characterized by sudden and excruciating pain of the affected joint and impairment of patients' quality of life. It is a combination of metabolic and inflammatory diseases [1]. Hyperuricemia is a prerequisite for the development of gout.

According to recent studies, gout and hyperuricemia have been reported to increase rapidly worldwide, and the resulting socio-economic burden including medical expense is also considerably increasing [2,3]. Accurate epidemiologic information on gout or hyperuricemia is essential for appropriate use of limited medical resources.

The patients with gout and hyperuricemia are at risk for developing a variety of comorbidities such as hypertension, chronic kidney disease (CKD), or metabolic syndrome [4]. There are also a few reports that gout or hyperuricemia is associated with variable degree of risk for neurodegenerative diseases, compromised bone health, or cancer. However, the causal relationship between gout and these comorbidities are still unclear, especially in the Korean population.

Gout is a disease that requires lifelong management. It is one of the diseases that have not been properly treated although many treatment guidelines have been published to provide optimal treatment in each country [5].

This review summarizes the epidemiology and treatment-related problems of gout and hyperuricemia as well as related con-

**Received** December 15, 2022; **Revised** March 15, 2023; **Accepted** March 20, 2023, **Published online** April 1, 2023

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ditions in Korea by comparing to those in other countries. The author selected relevant articles on epidemiology and treatment of gout and hyperuricemia published between January 2003 and August 2022 in PubMed, Korea Citation Index, and homepage of Journal of Rheumatic Diseases.

## MAIN SUBJECTS

### Prevalence of hyperuricemia

Although the prevalence of hyperuricemia varied according to different regions and ethnicities, most studies are consistent with the incremental trend of hyperuricemia (Figure 1) [6-9]. In Korea, there have been several studies on hyperuricemia (Table 1 and Figure 1). A cohort study has reported that a seven-year cumulative incidence of hyperuricemia was 23.1% in Korean male workers of 30~59 years of age in one of the largest semiconductor manufacturing companies in Korea [10]. The prevalence of hyperuricemia in 2002 was 9.3% among those who participated in the health check-up program [11]. A single-center study in a sample of 2,297 participants reported that the prevalence of hyperuricemia between 2008 and 2010 was 9.8% [12]. These two studies reported similar prevalence of hyperuricemia, which had a common point in that they used the same definition of hyperuricemia as the examinees of health checkup center of the tertiary hospital. Two epidemiological studies using the national surveillance data also gave report regarding the prevalence of hyperuricemia in Korean population. The age-standardized prevalence of hyperuricemia has been estimated at 11.4% in the 2016 Korean National Health and Nutrition Examination survey (KNHANES) data [13]. The overall prevalence of hyperuricemia was 5.1% based on the data collected between 2004 and 2013 from the Korean Genome and Epidemiology Study [14]. As shown in Table 1, the prevalence of hyperuricemia varies, ranging from 5.1% to 11.4% in Korea. The discrepancies among these studies might be due to the differences in the definition of hyperuricemia, duration of data collection, estimate methodology, and timeframe of the study. Overall, the prevalence of hyperuricemia in Korea tends to increase over the years as in other countries worldwide, but a relatively faster increase in women than that in men was observed in Korea. The increasing prevalence of hyperuricemia has been perceived as an emerging public health concern worldwide.

### Prevalence of gout

Reported estimates of gout prevalence range from 2.7% to 6.7% in countries (Figure 2) [6,15-19]. The most recent estimate

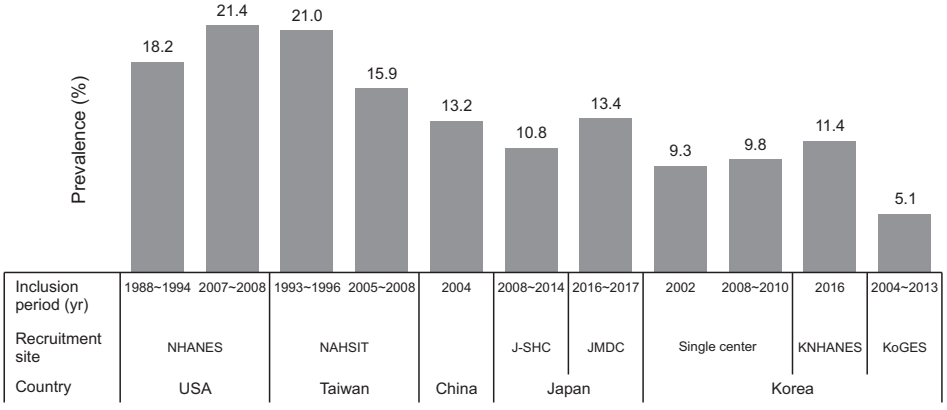


**Figure 1.** Worldwide prevalence ranges of hyperuricemia by country and time. JMDC: Japan Medical Data Center, J-SHC: Japan Specific Health Checkups study, KNHANES: Korean National Health and Nutrition Examination Survey, KoGES: Korean Genome and Epidemiology Study, NAHSIT: Nutrition and Health Survey in Taiwan, NHANES: National Health and Nutrition Examination Survey.

**Table 1.** The prevalence of hyperuricemia in Korea

| Reference | Year of publication | Years timeframe | Participants (n) | Definition of hyperuricemia | Prevalence (%) | | |
|---|---|---|---|---|---|---|---|
| | | | | | Overall | Men | Women |
| [11] | 2004 | 2002 | 6,461 | | 9.3 | 14.3 | 2.2 |
| [12] | 2012 | 2008~2010 | 2,297 | SUA ≥7 mg/dL in men and ≥6 mg/dL in women | 9.8 | 15.0 | 4.1 |
| [13] | 2018 | 2016 | 5,548 | | 11.4 | 17.0 | 5.9 |
| [14] | 2021 | 2004~2013 | 172,970 | SUA level ≥7.0 mg/dL | 5.1 | 13.3 | 0.8 |

SUA: serum uric acid.

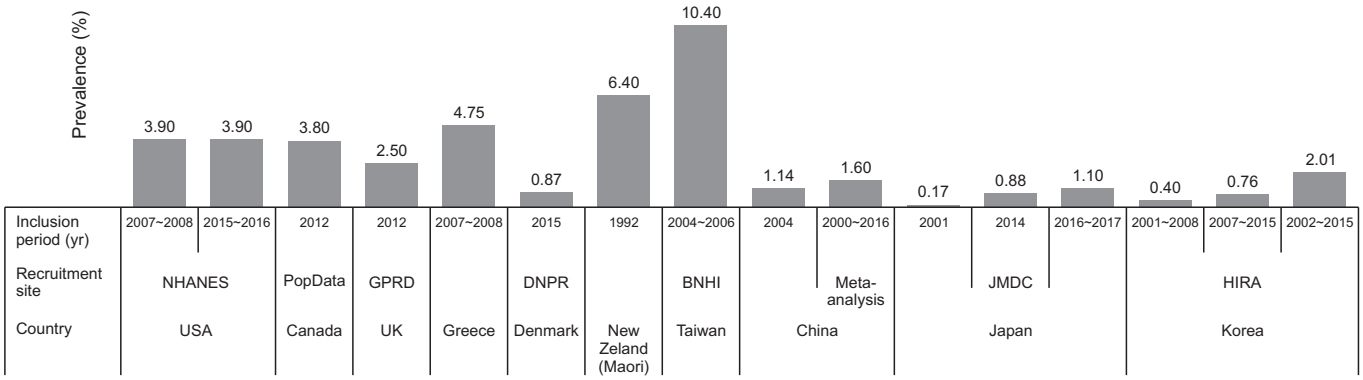


**Figure 2.** Worldwide prevalence ranges of gout by country and time. BNHI: Bureau of National Health Insurance, DNPR: Danish National Patient Register, GPRD: General Practice Research Database, HIRA: Health Insurance Review & Assessment data, JMDC: Japan Medical Data Center, NHANES: National Health and Nutrition Examination Survey, PopData: PopulationData BC (British Columbia).

**Table 2.** Epidemiologic studies of the prevalence of Korean patients with gout using national health claims database

| Reference | Year of publication | Study population | Data collection time | Gout diagnosis | Prevalence (%) | | |
|---|---|---|---|---|---|---|---|
| | | | | | Overall | Men | Women |
| [25] | 2011 | All beneficiaries | 2001~2008 | | 0.40 | 0.71 | 0.08 |
| [26] | 2017 | All beneficiaries | 2007~2015 | Physician-diagnosed gout | 0.76 | 1.36 | 0.16 |
| [27] | 2020 | All beneficiaries | 2002~2015 | | 2.01 | 3.03 | 1.01 |

of the lifetime prevalence of a health professional-diagnosed gout in the USA was 3.9% (5.2% in men and 2.7% in women) in 2015~2016 [16]. On analyzing 2007~2016 National Health and Nutrition Examination Survey (NHANES) data by race, the prevalence of gout was 4.8%, 4%, and 2% in African Americans, Caucasians, and Hispanics, respectively [16]. Greece has the highest prevalence of gout in Europe, approaching 4.75% of the adult population [17]. In a nationwide register-based retrospective study during the 20-year study period (1995~2015) in Denmark, the estimated prevalence of gout was 0.6% in 2000, with a significant increase, up to 0.87% in 2015, an increase by approximately 45% over 15 years [19].

As shown in Figure 2, gout is particularly prevalent in Taiwan aborigines and Polynesian peoples [20,21]. Thus, genetic variation may partly explain the higher prevalence of gout in this region. In a meta-analysis of studies reported between 2000 and 2016, the pooled estimate of gout prevalence was 1.6% in China, varying from 0.8% to 5% by regions [22]. The overall prevalence for physician-diagnosed gout was 1.14% in Eastern China [23]. In the study using Japan Medical Data Center database, the prevalence of gout was 0.82% in 2010, with a slight increase, up to 0.88% in 2014 (1.66% in men and 0.09% in women) [24]. In a cross-sectional study using Japanese claims database, the prevalence of gout was 1.1% (1.9% in men and less than 0.1% in women) [8].

In Korea, three epidemiological studies using the Health Insurance Review & Assessment (HIRA) data reported the prevalence of gout (Table 2 and Figure 2). In the HIRA database over the period 2001–2008, the prevalence of gout was 0.17% in 2001 and 0.40% in 2008, with a 2.3-fold increase over seven years [25]. In the Korean claims database for the period 2007~2015, the prevalence of gout was significantly higher in 2015 than that in 2007, with an approximately 2.3-fold increase from 0.35% in 2007 to 0.76% in 2015 [26]. In the claims database for the period 2002~2015, the prevalence of gout increased approximately five-fold, from 0.39% in 2002 to 2.01% in 2015 [27]. Although significant differences in its prevalence were found among three nationwide population studies, the rate of increase in prevalence between 2007 and 2015 was almost similar, suggesting that gout prevalence continued to increase in Korea rapidly and significantly over the past eight years.

Globally, including Korea, it is common that gout is frequent in advanced age or middle-aged men. The prevalence of gout in Korea seems to be lower than that in Western developed countries and Taiwan. As shown in Figure 2, recent estimates indicate that the prevalence of gout seems to have reached a plateau in

North America while it seems to continue to increase rapidly in Europe and Asia.

## The risk of comorbidities in gout or hyperuricemia

Serum uric acid (SUA) has been known to be a double-edged sword with pro-inflammatory as well as antioxidant effects in the body. Gout is a common hyperuricemic metabolic condition that is complicated by an increased burden of various comorbidities.

According to the third NHANES, gout is associated with increased prevalence of coexistent hypertension, obesity, diabetes mellitus, CKD, myocardial infarction (MI), heart failure, and stroke [28]. Similarly, using the National Health Insurance Service (NHIS) database, it was reported that Korean population with gout had increased risks for acute MI, ischemic heart disease, and cardiovascular (CV) disease, in descending order [29]. In each study conducted at the same tertiary hospital in 2004 and 2016, respectively, the frequency of metabolic syndrome in gout patients showed a trend towards an increase in 2016 compared to that in 2004 (50.8 vs. 42.2%) [30,31]. The Korean population with gout was associated with an increased prevalence of hypertension (79%), obesity (49%), and diabetes mellitus/hyperglycemia (33%) [31]. Further, in an analysis using the NHIS database, the prevalence of metabolic syndrome in the Korean population with gout was significantly higher than that in the control group (44% vs. 5.2%) [32].

There are multiple studies on the relationship between SUA levels and mortality. In all inhabitants of Japan who were between 40 and 74 years of age, all-cause and CV mortality rates in participants with hyperuricemia were significantly increased compared with those with normouricemia (hazard ratio [HR], 1.36; 95% confidence interval [CI], 1.25~1.49 for all-cause mortality and HR, 1.69; 95% CI, 1.41~2.01 for CV mortality) [7]. The burden of death attributable to hyperuricemia in Korea is not well quantified. In a large-scale cohort study in Korea, adults in the highest SUA categories (≥9.5 mg/dL for men and ≥8.5 mg/dL for women) were 2.39 (95% CI, 1.57~3.66) in men and 3.77 (95% CI, 1.17~12.17) in women for all-cause mortality, respectively, suggesting that a substantial number of all-cause deaths were attributed to hyperuricemia [33]. Management of various comorbidities in the Korean population with gout or hyperuricemia needs to be considered.

## Clinical association between gout or hyperuricemia and neurodegenerative disease

Previous studies have reported that uric acid may be one of

**Table 3.** The risk of dementia and Parkinson's disease in patients with gout or hyperuricemia

| Reference | Year of publication | Country | Study design and population | Results |
|---|---|---|---|---|
| Dementia | | | | |
| [36] | 2016 | - | Meta-analysis | A weak association between SUA and dementia |
| [37] | 2018 | France | A population-based cohort study (n=4,931) | Increased risk of dementia in elder people with high SUA (HR, 1.79; 95% CI, 1.17~2.73) |
| [40] | 2022 | Korea | A nationwide population-based cohort study (n=5,052 with gout) | Decreased risk of the risk of incident Alzheimer's disease in gout, especially in elderly patients (HR, 0.73; 95% CI, 0.54~0.98) |
| Parkinson's disease | | | | |
| [35] | 2017 | - | Meta-analysis | A significantly lower mean concentration of SUA in patients with PD compared to controls |
| [38] | 2019 | USA | A study of U.S. Medicare data (n=1.72 million) | Increased risk of PD in gout (HR, 1.14; 95% CI, 1.07~1.21), with the risk being significant in the group of 65~75 years of age |
| [41] | 2020 | Taiwan | Nationwide Population-Based Cohort Study (n=7,900 with gout) | No protective effect of gout for the risk of PD (HR, 1.01; 95% CI, 0.93~1.31) |
| [39] | 2021 | Korea | Nationwide Population-Based Cohort Study (n= 327,160 with gout) | No clinical association between Gout and PD (HR, 1.00; 95% CI, 0.91~1.10) |

CI: confidential interval, HR: hazard ratio, PD: Parkinson's disease, SUA: serum uric acid.

the most important antioxidants in the blood. There are studies on the association between gout or SUA level and several neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis (Table 3) [34-41]. There was no consistent relationship between SUA level and dementia or cognitive impairment based on a meta-analysis [36]. Risk of dementia, especially vascular or mixed dementia, may be increased with high SUA levels in elderly people [37]. Few studies have explored the association between gout or hyperuricemia and neurodegenerative diseases in Korea [39,40]. In a retrospective cohort study using Korea NHIS data, gout has been shown to be inversely related to the risk for overall dementia, especially in elderly men. On the other hand, after adjusting for age and sex, the risk for vascular dementia in gout patients increased by approximately 2.3 times in non-elderly men. In this study, the association between gout and dementia showed different results according to age or type of dementia [40]. Studies on the association between gout or hyperuricemia and Parkinson's disease have also yielded conflicting results. In a meta-analysis, hyperuricemia significantly reduced the risk for Parkinson's disease, and the SUA level tended to decrease as the disease progresses [35]. Based on the US Medicare data between 2006 and 2012, hyperuricemia increased the risk for incidental Parkinson's disease by 27% in elderly people [38]. Furthermore, a population-based retrospective cohort study in Taiwan did not reveal any significant results between gout and Parkinson's disease [41]. Similar to that of a previous Taiwan study, the Korean patients with gout were not associated with an increased risk for Parkinson's disease in a nationwide population-based cohort [39]. One of the limitations of this study may be the lack of adjustment for various confounding factors that may affect dementia considering the inherent nature of NHIS database. Considered together, although the association between hyperuricemia or gout and neurodegenerative diseases has been investigated in various published studies, their causal relationship is still unclear.

## Cancer risk in patients with gout

The pro-oxidant and anti-oxidant properties of uric acid have been postulated to play an important role in tumorigenesis [42]. For example, a study of US veterans reported that the 10-year prevalence of colorectal cancer was significantly lower among gout patients than that in osteoarthritis patients despite the adjustment for the use of colchicine, allopurinol, and/or non-steroidal anti-inflammatory drugs [43]. Based on the National Health Insurance Database in Taiwan, the risk for overcall cancer was 1.15-time elevated among patients with gout [44]. Furthermore, analysis of Swedish nationwide hospital discharge system identified 1.25-time higher risk to develop cancer in gout patients [45]. In a meta-analysis, hyperuricemia or gout was associated with higher cancer incidence and mortality [46]. Recently, two nationwide population-based studies reported regarding the cancer risk in Korean patients with gout [47,48]. Overall, the cancer risk was 1.2-time higher in middle-aged patients with gout compared to that in controls, while the all-cause mortality and cancer mortality were 1.5-time higher. In the sub-analysis of cancer subtype, the risk was increased in the order of gastric cancer, head and neck cancer, and hematologic malignancy. The risk for colon cancer was 30% lower in gout patients but was of borderline significance [48]. The other study using database from 2011~2015 reported overall cancer risk was weakly significant among those ≥20 years of age with gout (HR, 1.05; 95% CI, 1.03~1.08) [47]. The risk for stomach cancer was similarly increased in both studies, but the risk for other cancer types, including head and neck cancer, colon cancer, and hematologic malignancy, showed conflicting results between the two studies. One of the reasons for this difference is that the study of Lee et al. [48] was restricted to the patients of 41–55 years of age with gout. Considered together, although the risk for specific cancer type including colorectal cancer is conflicting in gout patients, it is considered a common opinion that the overall risk for cancer is increased in gout patients. It is difficult to give a definite cause for the increased risk of cancer in patients with gout. As one of the various reasons, the pro-inflammatory properties of uric acid have been postulated to play an important role in the pathogenesis of cancer. Also, gout sits at the intersection of inflammatory disease and metabolic disease such as diabetes, hypertension, hyperlipidemia, and obesity. These metabolic diseases are also associated with excess cancer, and chronic inflammation [42]. These may be an important link between gout and the development of cancer.

## Other disease associations with hyperuricemia

Many studies have been reported on the impact of SUA on various diseases [33-40,44-58]. For example, higher SUA levels were related to a reduced risk for lower urinary tract symptoms and was positively associated with lung function among clinically healthy middle-aged men [49,53]. On the contrary, hyperuri-

cemia was associated with decreased lung function in the female general population [55]. In addition, a cross-sectional study demonstrated a positive association in men between SUA and lumbar spine bone mineral density (BMD), while Mendelian randomization analysis did not support a causal association between SUA level and lumbar spine or femur neck BMD [52,56]. Higher SUA level may have opposing effects depending on tissue type, sex, and age. Further studies are necessary to confirm and explain the relationship between specific disease conditions and hyperuricemia.

## Disease burden of gout

A systematic review on the economic burden of gout found that it ranged from $172 to $6,179, depending on population characteristics [59]. This showed positive associations of direct medical costs with SUA level, attack frequency, or presence of tophi [59]. The estimated economic burden for new cases of acute gout is reported to be $27 million yearly in the US [60]. In a cross-sectional study, patients with uncontrolled gout had higher total medical costs than those with well-controlled gout and without gout [61]. These results suggest that medical costs can be reduced by controlling the acute gout attacks. The economic burden of gout is most easily assessed in patients with acute gouty attack, resulting in emergency department visits, hospitalization, and work productivity loss [2]. However, the burden of illness of gout is not well documented in Korea. Recently, a study reported a large increase in hospital visits for gout between 2010 and 2017, especially emergency department visit, in Korea. Before 2013, the number of emergency room visits was high in the elderly over 70 years old, but after 2013, the number of visits to the relatively young middle-aged people of 30~50 years of age was the highest [62]. The most frequent visit to emergency room was among those in their 40s who were socially active and concerned of increase in healthcare resource utilization and indirect medical costs. In addition, care by rheumatologists for gouty attack is reported to reduce the economic burden [60]. The substantial economic burden may be attributed to increasing prevalence of gout and suboptimal treatment. These suggest that rheumatologists have an important role to play in reducing the economic cost of gout care despite methodologic limitations.

## Impact of weight change on SUA level in Korean patients

Currently, many countries have published gout treatment guidelines that suit their medical environment. Many guidelines recommend weight reduction as a non-pharmacologic measure for gout management despite the lack of sufficient data to support the possible decrease of SUA levels by weight reduction. Recent studies have confirmed that weight loss, achieved by dietary intervention or bariatric surgery, is effective in reducing SUA levels [63-65]. Among men with high CV risk observed over a seven-year period, the effect of weight reduction of ≥10 kg on achieving target level increased by approximately four-fold and its corresponding SUA level change was –0.62 mg/dL [64]. A retrospective observational study for the association between each body composite and SUA level was recently published based on clinically apparent healthy Korean participants [66,67]. The impact of fat mass change on SUA levels was modest, as every 1-kg fat mass reduction correlated to a 0.06-mg/dL decrease in SUA levels among clinically apparently healthy men [66]. Further, as body mass index (BMI) decreased by one unit, the probability of reaching the therapeutic target of SUA increased by 18% [67]. Although this study is a cross-sectional study and not an interventional study, it is the first study to analyze the relationship between change of body composite and alteration of SUA levels in the Korean population. Although the odds of these studies in achieving normouricemia were relatively small, this may provide the basis for healthcare providers to comment on the relationship between fat mass or BMI changes and SUA levels in men with asymptomatic hyperuricemia.

## Compliance of urate-lowering therapy in patients with gout

Gout still remains poorly managed in the general population. The prescription of urate-lowering therapy (ULT) is not adequately applied to the extent that only a third to half of patients with gout receive ULT [3]. Drug adherence in gout is reported to be among the poorest of several chronic diseases such as hypertension, diabetes, or rheumatoid arthritis [68]. One of the reasons for suboptimal treatment of gout is poor adherence to ULT. In a large retrospective claims analysis, 55% of patients with gout started allopurinol. Of these, more than 50% had a significant interruption in medication. The percentage of patients reaching target SUA levels (<6 mg/dL) was 49.3%~56.8% among the adherent participants and 22.5%~27.8% of non-adherent partici-

pants [69]. Adherence to ULT in patients with gout worldwide varied, ranging from 17% to 78% in prescription/claims studies [70]. Table 4 summarizes studies on the compliance of urate-lowering drugs in Korean patients with gout. Two prospective observational cohort studies were conducted in a tertiary hospital using pills monitored by the nurse, which showed higher adherence compared to those in previous studies [71,72]. The authors explained that the differences were due to study design (retrospective analyses vs. a prospective observational cohort study), willingness of volunteered patients, education about the rationale and goals of ULT, and prescription by rheumatologists rather than a primary care physician [71]. The adherence of ULT was reported to be 89.1% in a brief paper-based survey, which was conducted on patients with physician-diagnosed gout visiting the rheumatology outpatient clinics of 16 tertiary hospitals [73]. Factors related to good adherence included the elderly, better knowledge of gout management strategies, and the preference for ULT. Based on HIRA database 2007 to 2015, ULT was reported to be prescribed in more than 80% of Korean patients with gout [74]. Of these, only 35% of the patients were continuously prescribed ULT during five years. In summary, as shown in Table 4, adherence to ULT in Korea reported various results, ranging from 33% to 89.1%, according to study design or data collection time [71-74]. Even if gout is one of the curable rheumatic diseases using inexpensive and effective medications, appropriate treatment is not being performed worldwide, including Korea, suggesting that new measures are needed, along with continuous efforts to overcome poor compliance to ULT.

## Comparative CV risk among urate-lowering drugs in Korea

Urate-lowering drugs were grouped based on their mechanism of action. Urate-lowering drugs available in Korea are as follows: allopurinol, febuxostat, and benzbromarone. Despite effective ULT, potential serious adverse effects including allopurinol hypersensitivity syndrome (AHS) have become an obstacle to ULT use in the past. Recently, the use of febuxostat has raised concern in gout patients with high CV risk. There has been a debate whether febuxostat may increase the risk of CV events in gout patients [75,76]. In this regard, CARES trial results were reported in 2019. This caused febuxostat to be a second-line drug in patients with major CV disease, but subsequent studies after the CARES trial results have not replicated the result of the CARES trial [77-79]. Furthermore, for various reasons, it may be unreasonable to apply these evidences directly to Korean population with gout. In addition to several limitations of the CARES trial, only a small portion of Asians were included in this study. Further, using 2002~2015 Korean NHIS data, no significant difference in the risk for CV events and all-cause mortality between febuxostat and allopurinol users was reported after minimizing confounding [80], suggesting that there is no direct evidence that febuxostat increases the risk for CV disease in Korean patients with gout. Based on these findings, febuxostat has been still used as the first-line drug in Korean patients with gout. Some studies explain that the increase in CV events in gout is not due to the drug, but rather due to the rapid change in SUA level that occurs after ULT discontinuation or "sick-stopper" effect [81-83]. The controversy over the CV

**Table 4.** Compliance of ULT in Korean with gout

| Reference | Year of publication | Inclusion period | Adherence methods | Adherence to ULT | Comment |
|---|---|---|---|---|---|
| [71] | 2016 | 2015 | MPR | 71.2% | Prospective observational cohort study (n=132)<br>Rheumatology clinic of a tertiary hospital |
| [74] | 2018 | 2007~2015 | Prescription claims | 33% in 2007 to 2012 period<br>38% in 2010 to 2015 period | Nationwide Population-Based Cohort Study |
| [72] | 2019 | 2013~2014 | MPR | 71.8% at 1 year<br>65.5% at 2 year<br>58.2% at 3 year | Prospective observational cohort study, (n=220)<br>Rheumatology clinic of a tertiary hospital |
| [73] | 2021 | 2020 | Self-reported | 89.1% | Rheumatology clinics of 16 tertiary hospitals (n=809) |

MPR: medication possession ratio, ULT: urate lowering therapy.

**Table 5.** Further research agenda of gout and hyperuricemia treatment in Korea based on this review

| |
|---|
| 1. Development of a gout diet and lifestyle program specialized for Korean gout patients |
| 2. Development of program in enabling adherence and improving gout care in Korean |
| 3. Potential effect of urate lowering therapy on cardiorenal comorbidities in Korean patients with gout |
| 4. Controversy on cardiovascular risk or mortality of urate lowering therapy including febuxostat in Korean patients with gout |
| 5. Identification of patients profiles to prevent allopurinol induced severe cutaneous adverse reactions in Korean |

risk of febuxostat is ongoing. Meanwhile, two population-based retrospective cohort studies comparing the CV risk between allopurinol and benzbromarone showed different results. A retrospective cohort study using NHIS data between 2002 and 2017 found that benzbromarone may reduce CV risk and all-cause mortality by 22% and 66% compared to allopurinol [84]. In contrast, the other study did not find a significant difference in CV risk despite that the same NHIS database was used [85]. The conflicting results may be attributed to differences in data collection times and operational definitions of gout and outcomes. Considered together, it would be necessary to obtain information on various complications, including CV safety, with each ULT, and to prescribe drugs considering these safety profiles in the future.

### The utility of *HLA-B*58:01* allele and febuxostat in gout patients with CKD

The *HLA-B*58:01* allele is known to be associated with a markedly elevated risk for AHS. The *HLA-B*58:01* is present in approximately 7%~12% of Korean population with CKD, which is relatively higher than that of 0.7% of Caucasian and Hispanics [86-88]. It was demonstrated *HLA-B*58:01* screening test before allopurinol imitation could considerably reduce the occurrence of AHS in Korean gout patients with CKD [88,89]. Also, 2020 American College of Rheumatology gout clinical practice guidelines conditionally recommended that, in subgroups of African and Southeast Asian ethnicities including Korean populations, *HLA-B*58:01* tests should be performed to prevent AHS before starting allopurinol [90]. These will be included in the Korean College of Rheumatology guidelines for the management of gout in the future. Considering the increasing risk for AHS, and the higher prevalence of *HLA-B*58:01* in Koreans with CKD, febuxostat might be positioned as a good alternative to replace allopurinol in Korea. However, the safety of febuxostat in gout patients with moderate-to-severe renal impairment has not been established. To answer these questions, there are two studies comparing the efficacy and tolerability of febuxostat in gout patients with CKD. Febuxostat was reported to be efficacious and well-tolerated in CKD in not only stage 3, but also in stage 4/5 patients [91]. After treatment with febuxostat for more than three months in Korean patients with gout on dialysis, the safety and effectiveness of febuxostat were acceptable [92]. In gout patients with CKD, an optimal treatment might be expected using the *HLA-B*58:01* test and febuxostat.

## CONCLUSION

The prevalence of gout and hyperuricemia are constantly increasing in Korea. It is necessary to understand the unique clinical picture of hyperuricemia or gout in Korea, for which, large-scale epidemiologic data are essential, including epidemiology, comorbidities, and treatment-related problems such as drug compliance in Korean patients with gout or hyperuricemia. Based on these factors, diagnosis and treatment guidelines should be developed in consideration of the medical situation in Korea. Korean College of Rheumatology has developed its first Korean guidelines for the management of gout under preparation for publication. As shown in Table 5, further investigations will provide necessary data to determine successful management strategies for Korean patients with gout or hyperuricemia.

## FUNDING

None.

## ACKNOWLEDGMENTS

None.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

## REFERENCES


1. Dalbeth N, Choi HK, Joosten LAB, Khanna PP, Matsuo H, Perez-Ruiz F, et al. Gout. Nat Rev Dis Primers 2019;5:69.
2. Wertheimer A, Morlock R, Becker MA. A revised estimate of the burden of illness of gout. Curr Ther Res Clin Exp 2013;75:1-4.
3. Dehlin M, Jacobsson L, Roddy E. Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors. Nat Rev Rheumatol 2020;16:380-90.
4. Choi HK, McCormick N, Yokose C. Excess comorbidities in gout: the causal paradigm and pleiotropic approaches to care. Nat Rev Rheumatol 2022;18:97-111.
5. Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Comparison of drug adherence rates among patients with seven different medical conditions. Pharmacotherapy 2008;28:437-43.
6. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum 2011;63:3136-41.
7. Otaki Y, Konta T, Ichikawa K, Fujimoto S, Iseki K, Moriyama T, et al. Possible burden of hyperuricaemia on mortality in a community-based population: a large-scale cohort study. Sci Rep 2021;11:8999.
8. Koto R, Nakajima A, Horiuchi H, Yamanaka H. Real-world treatment of gout and asymptomatic hyperuricemia: a cross-sectional study of Japanese health insurance claims data. Mod Rheumatol 2021;31:261-9.
9. Chuang SY, Lee SC, Hsieh YT, Pan WH. Trends in hyperuricemia and gout prevalence: Nutrition and Health Survey in Taiwan from 1993-1996 to 2005-2008. Asia Pac J Clin Nutr 2011;20:301-8.
10. Ryu S, Chang Y, Zhang Y, Kim SG, Cho J, Son HJ, et al. A cohort study of hyperuricemia in middle-aged South Korean men. Am J Epidemiol 2012;175:133-43.
11. Kim EH, Jeon K, Park KW, Kim HJ, Ahn JK, Jeon CH, et al. The prevalence of gout among hyperuricemic population. J Korean Rheum Assoc 2004;11:7-13.
12. Hong SJ, Kim YS, Kim HS. Prevalence and clinical features of hyperuricemia in Gwangju and Jeonnam territories. J Rheum Dis 2012;19:138-46.
13. Kim Y, Kang J, Kim GT. Prevalence of hyperuricemia and its associated factors in the general Korean population: an analysis of a population-based nationally representative sample. Clin Rheumatol 2018;37:2529-38.
14. Koo BS, Jeong HJ, Son CN, Kim SH, Kim HJ, Kim GH, et al. Distribution of serum uric acid levels and prevalence of hyper- and hypouricemia in a Korean general population of 172,970. Korean J Intern Med 2021;36(Suppl 1):S264-72.
15. Rai SK, Aviña-Zubieta JA, McCormick N, De Vera MA, Shojania K, Sayre EC, et al. The rising prevalence and incidence of gout in British Columbia, Canada: population-based trends from 2000 to 2012. Semin Arthritis Rheum 2017;46:451-6.
16. Chen-Xu M, Yokose C, Rai SK, Pillinger MH, Choi HK. Contemporary prevalence of gout and hyperuricemia in the United States and decadal trends: the National Health and Nutrition Examination Survey, 2007-2016. Arthritis Rheumatol 2019;71:991-9.
17. Anagnostopoulos I, Zinzaras E, Alexiou I, Papathanasiou AA, Davas E, Koutroumpas A, et al. The prevalence of rheumatic diseases in central Greece: a population survey. BMC Musculoskelet Disord 2010;11:98.
18. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. Ann Rheum Dis 2015;74:661-7.
19. Zobbe K, Prieto-Alhambra D, Cordtz R, Højgaard P, Hindrup JS, Kristensen LE, et al. Secular trends in the incidence and prevalence of gout in Denmark from 1995 to 2015: a nationwide register-based study. Rheumatology (Oxford) 2019;58:836-9.
20. Klemp P, Stansfield SA, Castle B, Robertson MC. Gout is on the increase in New Zealand. Ann Rheum Dis 1997;56:22-6.
21. Tu FY, Lin GT, Lee SS, Tung YC, Tu HP, Chiang HC. Prevalence of gout with comorbidity aggregations in southern Taiwan. Joint Bone Spine 2015;82:45-51.
22. Huang J, Ma ZF, Zhang Y, Wan Z, Li Y, Zhou H, et al. Geographical distribution of hyperuricemia in mainland China: a comprehensive systematic review and meta-analysis. Glob Health Res Policy 2020;5:52.
23. Kuo CF, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. Nat Rev Rheumatol 2015;11:649-62.
24. Hakoda M, Kasagi F. Increasing trend of asymptomatic hyperuricemia under treatment with urate-lowering drugs in Japan. Mod Rheumatol 2019;29:880-4.
25. Lee CH, Sung NY. The prevalence and features of Korean gout patients using the National Health Insurance Corporation database. J Rheum Dis 2011;18:94-100.
26. Kim JW, Kwak SG, Lee H, Kim SK, Choe JY, Park SH. Prevalence and incidence of gout in Korea: data from the national health claims database 2007-2015. Rheumatol Int 2017;37:1499-506.
27. Park JS, Kang M, Song JS, Lim HS, Lee CH. Trends of gout prevalence in South Korea based on medical utilization: a National Health Insurance Service database (2002~2015). J Rheum Dis 2020;27:174-81.
28. Choi HK, Ford ES, Li C, Curhan G. Prevalence of the metabolic syndrome in patients with gout: the Third National Health and Nutrition Examination Survey. Arthritis Rheum 2007;57:109-15.
29. Moon KW, Kim MJ, Choi IA, Shin K. Cardiovascular risks in Korean patients with gout: analysis using a National Health Insurance Service database. J Clin Med 2022;11:2124.
30. Rho YH, Choi SJ, Lee YH, Ji JD, Choi KM, Baik SH, et al. Prevalence of the metabolic syndrome in patients with gout. J Korean Rheum Assoc 2004;11:349-57.
31. Jung JH, Song GG, Ji JD, Lee YH, Kim JH, Seo YH, et al. Metabolic syndrome: prevalence and risk factors in Korean gout patients. Korean J Intern Med 2018;33:815-22.
32. Rho YH, Choi SJ, Lee YH, Ji JD, Choi KM, Baik SH, et al. The prevalence of metabolic syndrome in patients with gout: a multicenter study. J Korean Med Sci 2005;20:1029-33.
33. Cho SK, Chang Y, Kim I, Ryu S. U-shaped association between serum uric acid level and risk of mortality: a cohort study. Arthritis Rheumatol 2018;70:1122-32.
34. Abraham A, Drory VE. Influence of serum uric acid levels on prognosis and survival in amyotrophic lateral sclerosis: a meta-analysis. J Neurol 2014;261:1133-8.

35. Wen M, Zhou B, Chen YH, Ma ZL, Gou Y, Zhang CL, et al. Serum uric acid levels in patients with Parkinson's disease: a meta-analysis. PLoS One 2017;12:e0173731.
36. Khan AA, Quinn TJ, Hewitt J, Fan Y, Dawson J. Serum uric acid level and association with cognitive impairment and dementia: systematic review and meta-analysis. Age (Dordr) 2016;38:16.
37. Latourte A, Soumaré A, Bardin T, Perez-Ruiz F, Debette S, Richette P. Uric acid and incident dementia over 12 years of follow-up: a population-based cohort study. Ann Rheum Dis 2018;77:328-35.
38. Singh JA, Cleveland JD. Gout and the risk of Parkinson's disease in older adults: a study of U.S. Medicare data. BMC Neurol 2019;19:4.
39. Kim JH, Choi IA, Kim A, Kang G. Clinical association between gout and Parkinson's disease: a nationwide population-based cohort study in Korea. Medicina (Kaunas) 2021;57:1292.
40. Kim JH, Yim DH, Choi IA, Lee J, Park H, Eom SY. Impact of clinical association between gout and dementia: a nationwide population-based cohort study in Korea. Arthritis Care Res (Hoboken) 2022 May 23 [Epub]. DOI: 10.1002/acr.24959
41. Hu LY, Yang AC, Lee SC, You ZH, Tsai SJ, Hu CK, et al. Risk of Parkinson's disease following gout: a population-based retrospective cohort study in Taiwan. BMC Neurol 2020;20:338.
42. Fini MA, Elias A, Johnson RJ, Wright RM. Contribution of uric acid to cancer risk, recurrence, and mortality. Clin Transl Med 2012;1:16.
43. Slobodnick A, Krasnokutsky S, Lehmann RA, Keenan RT, Quach J, Francois F, et al. Colorectal cancer among gout patients undergoing colonoscopy. J Clin Rheumatol 2019;25:335-40.
44. Kuo CF, Luo SF, See LC, Chou IJ, Fang YF, Yu KH. Increased risk of cancer among gout patients: a nationwide population study. Joint Bone Spine 2012;79:375-8.
45. Boffetta P, Nordenvall C, Nyrén O, Ye W. A prospective study of gout and cancer. Eur J Cancer Prev 2009;18:127-32.
46. Xie Y, Xu P, Liu K, Lin S, Wang M, Tian T, et al. Hyperuricemia and gout are associated with cancer incidence and mortality: a meta-analysis based on cohort studies. J Cell Physiol 2019;234:14364-76.
47. Oh YJ, Lee YJ, Lee E, Park B, Kwon JW, Heo J, et al. Cancer risk in Korean patients with gout. Korean J Intern Med 2022;37:460-7.
48. Lee JS, Myung J, Lee HA, Hong S, Lee CK, Yoo B, et al. Risk of cancer in middle-aged patients with gout: a nationwide population-based study in Korea. J Rheumatol 2021;48:1465-71.
49. Song JU, Hwang J, Ahn JK. Serum uric acid is positively associated with pulmonary function in Korean health screening examinees. Mod Rheumatol 2017;27:1057-65.
50. Ahn JK, Hwang J, Hwang JH, Yoon WT, Chung PW, Ryu S. The association between serum uric acid and asymptomatic intracranial arterial stenosis in middle-aged Koreans. Nutr Metab Cardiovasc Dis 2018;28:14-22.
51. Hwang J, Hwang JH, Chung SM, Kwon MJ, Ahn JK. Association between serum uric acid and arterial stiffness in a low-risk, middle-aged, large Korean population: a cross-sectional study. Medicine (Baltimore) 2018;97:e12086.
52. Hwang J, Hwang JH, Ryu S, Ahn JK. Higher serum uric acid is associated with higher lumbar spine bone mineral density in male health-screening examinees: a cross-sectional study. J Bone Miner Metab 2019;37:142-51.
53. Hwang J, Ryu S, Ahn JK. Higher levels of serum uric acid have a significant association with lower incidence of lower urinary tract symptoms in healthy Korean men. Metabolites 2022;12:649.
54. Lee KW, Shin D. Concurrent presence of high serum uric acid and inflammation is associated with increased incidence of type 2 diabetes mellitus in Korean adult population. Sci Rep 2022;12:11000.
55. Jeong H, Baek SY, Kim SW, Park EJ, Kim H, Lee J, et al. Gender-specific association of serum uric acid and pulmonary function: data from the Korea National Health and Nutrition Examination Survey. Medicina (Kaunas) 2021;57:953.
56. Lee YH, Song GG. Uric acid level, gout and bone mineral density: a Mendelian randomization study. Eur J Clin Invest 2019;49:e13156.
57. Kim K, Kang K, Sheol H, Shin J, Sim Y, Yang T, et al. The association between serum uric acid levels and 10-year cardiovascular disease risk in non-alcoholic fatty liver disease patients. Int J Environ Res Public Health 2022;19:1042.
58. Janssens HJ, Arts PG, Schalk BW, Biermans MC. Gout and rheumatoid arthritis, both to keep in mind in cardiovascular risk management: a primary care retrospective cohort study. Joint Bone Spine 2017;84:59-64.
59. Rai SK, Burns LC, De Vera MA, Haji A, Giustini D, Choi HK. The economic burden of gout: a systematic review. Semin Arthritis Rheum 2015;45:75-80.
60. Kim KY, Ralph Schumacher H, Hunsche E, Wertheimer AI, Kong SX. A literature review of the epidemiology and treatment of acute gout. Clin Ther 2003;25:1593-617.
61. Flores NM, Nuevo J, Klein AB, Baumgartner S, Morlock R. The economic burden of uncontrolled gout: how controlling gout reduces cost. J Med Econ 2019;22:1-6.
62. Son KM, Kim JR, Park HA, Kim HA. Trends in hospital visits and healthcare costs of gout and seropositive rheumatoid arthritis in Korea from 2010 to 2017 using National Healthcare Claims. Korean J Intern Med 2022;37:681-90.
63. Nielsen SM, Bartels EM, Henriksen M, Wæhrens EE, Gudbergsen H, Bliddal H, et al. Weight loss for overweight and obese individuals with gout: a systematic review of longitudinal studies. Ann Rheum Dis 2017;76:1870-82.
64. Zhu Y, Zhang Y, Choi HK. The serum urate-lowering impact of weight loss among men with a high cardiovascular risk profile: the Multiple Risk Factor Intervention Trial. Rheumatology (Oxford) 2010;49:2391-9.
65. Dalbeth N, Chen P, White M, Gamble GD, Barratt-Boyes C, Gow PJ, et al. Impact of bariatric surgery on serum urate targets in people with morbid obesity and diabetes: a prospective longitudinal study. Ann Rheum Dis 2014;73:797-802.
66. Ahn JK, Hwang J, Lee MY, Kang M, Hwang J, Koh EM, et al. How much does fat mass change affect serum uric acid levels among apparently clinically healthy Korean men? Ther Adv Musculoskelet Dis 2021;13:1759720X21993253.
67. Hwang J, Lee MY, Ahn JK, Cha HS. Relationship between changing body mass index and serum uric acid alteration among clinically apparently healthy Korean men. Arthritis Care Res (Hoboken) 2022;74:1277-86.
68. Perez-Ruiz F, Desideri G. Improving adherence to gout therapy: an expert review. Ther Clin Risk Manag 2018;14:793-802.
69. Halpern R, Mody RR, Fuldeore MJ, Patel PA, Mikuls TR. Impact of

noncompliance with urate-lowering drug on serum urate and gout-related healthcare costs: administrative claims analysis. Curr Med Res Opin 2009;25:1711-9.
70. Scheepers LEJM, van Onna M, Stehouwer CDA, Singh JA, Arts ICW, Boonen A. Medication adherence among patients with gout: a systematic review and meta-analysis. Semin Arthritis Rheum 2018;47:689-702.
71. Lee S, So MW. Adherence with urate-lowering therapies among male patients with gout in a routine clinical setting. Mod Rheumatol 2016;26:950-5.
72. Lee S, So MW, Ahn E. Long-term adherence and persistence with febuxostat among male patients with gout in a routine clinical setting. Mod Rheumatol 2019;29:662-8.
73. Chung MK, Kim SS, Cheon YH, Hong SJ, Choi HJ, Seo MR, et al. Patient perspectives and preferences regarding gout and gout management: impact on adherence. J Korean Med Sci 2021;36:e208.
74. Kim JW, Kwak SG, Park SH. Prescription pattern of urate-lowering therapy in Korean gout patients: data from the national health claims database. Korean J Intern Med 2018;33:228-9.
75. Schumacher HR Jr, Becker MA, Wortmann RL, Macdonald PA, Hunt B, Streit J, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. Arthritis Rheum 2008;59:1540-8.
76. Becker MA, Schumacher HR Jr, Wortmann RL, MacDonald PA, Eustace D, Palo WA, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med 2005;353:2450-61.
77. Mackenzie IS, Ford I, Nuki G, Hallas J, Hawkey CJ, Webster J, et al. Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial. Lancet 2020;396:1745-57.
78. Pawar A, Desai RJ, Liu J, Kim E, Kim SC. Updated assessment of cardiovascular risk in older patients with gout initiating febuxostat versus allopurinol. J Am Heart Assoc 2021;10:e020045.
79. Zhang M, Solomon DH, Desai RJ, Kang EH, Liu J, Neogi T, et al. Assessment of cardiovascular risk in older patients with gout initiating febuxostat versus allopurinol: population-based cohort study. Circulation 2018;138:1116-26.
80. Kang EH, Choi HK, Shin A, Lee YJ, Lee EB, Song YW, et al. Comparative cardiovascular risk of allopurinol versus febuxostat in patients with gout: a nation-wide cohort study. Rheumatology (Oxford) 2019;58:2122-9.
81. Lee JS, Oh JS, Kim YG, Lee CK, Yoo B, Hong S. Rapid reduction in uric acid by a urate-lowering agent is associated with recurrent cardiovascular events. Med Hypotheses 2020;141:109740.
82. Ghang BZ, Lee JS, Choi J, Kim J, Yoo B. Increased risk of cardiovascular events and death in the initial phase after discontinuation of febuxostat or allopurinol: another story of the CARES trial. RMD Open 2022;8:e001944.
83. Kolandaivelu K, Leiden BB, O'Gara PT, Bhatt DL. Non-adherence to cardiovascular medications. Eur Heart J 2014;35:3267-76.
84. Kang EH, Park EH, Shin A, Song JS, Kim SC. Cardiovascular risk associated with allopurinol vs. benzbromarone in patients with gout. Eur Heart J 2021;42:4578-88.
85. Eun Y, Han H, Kim K, Kang S, Lee S, Kim H, et al. Cardiovascular risk associated with allopurinol or benzbromarone treatment in patients with gout. Ther Adv Musculoskelet Dis 2022;14:1759720X221116409.
86. Lee KW, Oh DH, Lee C, Yang SY. Allelic and haplotypic diversity of HLA-A, -B, -C, -DRB1, and -DQB1 genes in the Korean population. Tissue Antigens 2005;65:437-47.
87. González-Galarza FF, Takeshita LY, Santos EJ, Kempson F, Maia MH, da Silva AL, et al. Allele frequency net 2015 update: new features for HLA epitopes, KIR and disease and HLA adverse drug reaction associations. Nucleic Acids Res 2015;43(Database issue):D784-8.
88. Park DJ, Kang JH, Lee JW, Lee KE, Wen L, Kim TJ, et al. Cost-effectiveness analysis of HLA-B5801 genotyping in the treatment of gout patients with chronic renal insufficiency in Korea. Arthritis Care Res (Hoboken) 2015;67:280-7.
89. Park HW, Kim DK, Kim SH, Kim S, Chae DW, Yang MS, et al. Efficacy of the HLA-B 58:01 screening test in preventing allopurinol-induced severe cutaneous adverse reactions in patients with chronic renal insufficiency-a prospective study. J Allergy Clin Immunol Pract 2019;7:1271-6.
90. FitzGerald JD, Dalbeth N, Mikuls T, Brignardello-Petersen R, Guyatt G, Abeles AM, et al. 2020 American College of Rheumatology guideline for the management of gout. Arthritis Rheumatol 2020;72:879-95. Erratum in: Arthritis Rheumatol 2021;73:413.
91. Ahn E, Lee S, Lee HN, Lee SG, So MW. Comparison of efficacy and safety of febuxostat in gout patients with chronic kidney disease stage 3 and stage 4/5. J Rheum Dis 2019;26:118-23.
92. Choi SY, Choi SW, Lee S, So MW, Oh JS, Lim DH. Efficacy and tolerability of febuxostat in gout patients on dialysis. Intern Med J 2021;51:348-54.