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Figure. 1. Cardiovascular event associated with initiating allopurinol and febuxostat - acute gout attack and cardiovascular gout attack

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Background: When serum uric acid rapidly increases or decreases due to such as alcohol consumption or fasting, free urate crystals are formed, which induce an acute joint inflammation referred to as an acute gout attack. In 86.4% of patients with gout, dual energy computed tomography demonstrated the deposition of urate crystals in vasculature, and urate crystals have been observed in coronary arteries and various tissues in 10.9% of patients with a heart transplant. However, whether hyperuricemia and urate crystal directly cause cardiovascular disease is not well known. We previously reanalyzed the CARES trial to calculate the mortality rates based on the median duration of exposure to study drugs and the median follow-up duration. A sharp increase in mortality was observed after allopurinol and febuxostat were discontinued. Even in view of the Sick-Stopper Effect, for about 40-fold increase in mortality following drug discontinuation, we postulated that the sharp increase in mortality may be associated with rapid changes in uric acid level (rebound hyperuricemia), and that withdrawal of hypouricemic agent leads to an acute inflammatory response due to an abrupt increase in serum uric acid level with subsequent free urate crystal formation in the cardiovascular system (cardiovascular gout attack)(1).

Objectives: Based on this hypothesis that some cardiovascular events may be cardiovascular gout attacks, we investigated the association between the cardiovascular event and initiation of hypouricemic agent, when is accompanied by acute gout attack and/or fluctuation of uric acid, in gout patients.

Methods: Using the Korean National Health Insurance Service (KNHIS) database, which covers the entire Korean population, we conducted a population-based cohort study among gout patients who initiated allopurinol or febuxostat between 2012 and 2018. The initiators were defined as those who had no prior dispensing of any urate-lowering therapy for at least 60 months before the first dispensing date (i.e. index date) of either allopurinol or febuxostat. We excluded patients with a diagnosis of cancer and patients treated with benzbramone. We investigated a composite cardiovascular event of hospitalized myocardial infarction, ischemic stroke, and cerebral hemorrhage. Fast forward. 

Results: We identified hospitalizations for cardiovascular event (acute myocardial infarction (n = 4338), cerebral infarction (n = 5127), and cerebral hemorrhage (n = 1593)) that occurred within 2 year before and 2 year after initiation of allopurinol or febuxostat. Of these, 4333 cardiovascular event (0.014 per person-time, 95% confidence interval [CI], 0.014 to 0.015) occurred in 2 years before initiation of allopurinol or febuxostat. 1932 cardiovascular event (0.081 per person-time, 95% confidence interval [CI], 0.076 to 0.086) occurred in 30 days before initiation of allopurinol or febuxostat. And, 83 cardiovascular event (0.030 per person-time, 95% CI, 0.024 to 0.037) occurred in 7 days after initiation of allopurinol or febuxostat. (Figure) 

Conclusion: Initiation of febuxostat and allopurinol was significantly associated with acute myocardial infarction, cerebral infarction, and cerebral hemorrhage. Considering that allopurinol and febuxostat usually are initiated a few weeks after a acute gout attack. Acute gout attack and/or fluctuation of uric acid level might be significantly associated with cardiovascular event. Some cardiovascular events might be cardiovascular gout attack.


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Figure. The cardiovascular event in gout patients who initiated and discontinued allopurinol and febuxostat.

OP0169 AMPUTATION PROCEDURES IN PATIENTS WITH GOUT COMPARED TO PATIENTS WITH DIABETES

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Background: Gout is the most common inflammatory arthritis in the United States (U.S.) and is associated with specific comorbidities, including hypertension, renal disease, cardiovascular disease, hyperlipidemia, and metabolic syndrome (1). This set of comorbidities is known for carrying an increased risk of macrovascular complications (e.g., myocardial infarction, stroke) and peripheral limb problems (e.g., skin ulcers, amputations). Diabetics are known to have an elevated risk of undergoing ulcer and amputation procedures, which have been shown to increase morbidity and mortality in this population (2,3). It is currently not known if patients with gout have an elevated independent risk for limb amputations or whether gout potentiates amputation rates in patients with diabetes.

Objectives: To assess and compare the rate of amputation procedures conducted in patients with gout, diabetes, both gout and diabetes, and neither gout nor diabetes.

Methods: In September 2019, a large U.S. claims database (includes data from 190 million patients over 7 years, TrinNetX "Diamond" network) was used to determine amputation rates in patients with gout and diabetes, TrinNetX only provides aggregate data and statistical summaries of de-identified patient information. Initial cohorts were developed to understand the amputation rate in patients with gout, regardless of diabetes comorbidity (n=4,467,721), and the amputation rate in patients with diabetes, regardless of gout comorbidity (n=25,972,726). Subsequently, the following four cohorts were constructed to isolate the two diseases: 1) presence of gout without diabetes (n=2,471,430), 2) presence of diabetes without gout (n=23,976,435), 3) presence of both gout and diabetes (n=1,996,291), and 4) absence of both gout and diabetes (control cohort, n=44,705,645). Demographic features of these groups were tabulated and amputation (foot, toes, hand, fingers) rates were calculated using procedural codes reported in each group.

Results: The overall rate of amputations in patients with gout (0.434%) was similar to the amputation rate in patients with diabetes (0.484%). However, when separating these patients into distinct, non-overlapping cohorts, the amputation rate in patients with gout but not diabetes (0.162%) differed from the rate in patients with diabetes but not gout (0.461%). The control population (no gout or diabetes) had an amputation rate of 0.035%. Unexpectedly, patients with both gout and diabetes had an amputation rate of 0.770%, the highest of all groups examined.

Conclusion: Gout is increasingly being linked to unfavorable cardiovascular, renal, and metabolic complications. Our analysis showed that having gout also increased the likelihood of undergoing an amputation procedure. Patients with gout but not diabetes suffered an approximately 3-fold increase in amputations compared to patients without either disease. Additionally, patients with both gout and diabetes had a notably increased risk of amputation compared to patients with only diabetes (no gout). Because amputations are an unfavorable outcome associated with procedural complication risk and long-term sequelae, this apparent increased risk of amputation in patients with gout warrants further exploration.


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The cardiovascular event in gout patients who initiated and discontinued allopurinol and febuxostat.
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** OP0171 MENDANE RANDOMIZATION SHOWS NO CAUSAL ASSOCIATION BETWEEN SERUM URATE OR GOUT AND TYPE-2 DIABETES**

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**Background:** Positive associations between gout1,2 or serum urate (SU)3 and risk of type-2 diabetes (T2D) have been reported in population-based observational studies, but may be due to residual confounding. As such, causal roles of SU and gout on development of T2D are unclear.

**Objectives:** Use two-sample mendelian randomization to estimate the causal effects of SU and gout on T2D and glycemic traits.

**Methods:** Aggregate data from three large genome-wide association studies were used to identify genetic variants (SNPs) associated with the exposures and outcomes. Exposure SNPs were sourced from Global Urate Genetics Consortium (> 140,000 individuals); outcome SNPs sourced from DiABetes Genetics Replication And Meta-analysis consortium (DIAGRAM; > 34,000 T2D cases and > 114,000 controls) and Meta-Analyses of Glycine and Insulin-related traits Consortium (MAGIC; > 46,000 non-diabetics).

We analysed SNPs associated with SU levels (n=28) and gout (n=6) for associations with T2D and three glycemic traits (insulin resistance, fasting insulin levels, and HbA1c) using inverse variance weighted meta-analysis methods. We also specifically examined two SNPs mapping to the SLC2A9 gene, which encodes the GLUT9 transporter (for glucose and urate), estimating Wald ratios for these individual SNPs. Analyses were performed with TwoSampleMR package in R and mFinD power calculator.

**Results:** Estimated effects of genetically-determined gout on each of the four outcomes (T2D, insulin resistance, fasting insulin levels, and HbA1c) using inverse variance weighted meta-analysis methods. We also specifically examined two SNPs mapping to the SLC2A9 gene, which encodes the GLUT9 transporter (for glucose and urate), estimating Wald ratios for these individual SNPs. Analyses were performed with TwoSampleMR package in R and mFinD power calculator.

**Conclusion:** Evidence from this instrumental variable analysis suggests gout and SU are signals for future T2D, but neither SU or gout itself are causally associated with the development of this condition. As such, interventions targeting SU levels alone are unlikely to lower the risk of T2D.

**References:**

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** OP0172 EFFECT OF WEIGHT LOSS AND LIRAGLUTIDE ON SERUM URATE LEVELS AMONG OBESE KNEE OSTEOARTHRITIS PATIENTS: SECONDARY ANALYSIS OF A RANDOMISED CONTROLLED TRIAL**

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**Background:** There is a strong association between gout and obesity. Lowering urate is the cornerstone of gout management [1] and urate levels correlate strongly with central obesity. Previous studies suggest that weight loss has a positive effect on serum urate, however, the studies are sparse and small [2].

**Objectives:** To assess the impact of an initial low-calorie diet-induced weight loss and subsequent randomisation to the body weight-lowering drug liraglutide (a glucagon-like peptide 1 receptor agonist) on placebo on serum urate levels.

**Methods:** In theLOSE-IT trial (NCT02905864), a randomised, double-blind, placebo-controlled, parallel group, single-centre trial [3], 156 obese individuals with knee osteoarthritis, but without gout, were offered an initial 8-week intensive diet intervention period (week -8 to 0) on Cambridge Weight Plan (800-1000 kcal/day) followed by a weight loss maintenance period in which participants were randomised to either liraglutide 3 mg/day or placebo for 52 weeks. We conducted a secondary analysis of blood samples collected at week -8, 0 and 52. The primary outcome measure was change in serum urate. We used paired t-test for the change from week -8 to 0, and for change from week 0 to 52 we used an ANCOVA model adjusted for stratification factors (sex, age, category and obesity class), and the level of the outcome at baseline. Data were analysed as observed (i.e. no imputation of missing data).

**Results:** 156 individuals were randomised and 155 had blood samples taken at baseline. In the initial intensive diet intervention period (week -8 to 0) they lost a mean of 12.5 kg (95% CI -13.1 to -11.9; n = 156), whereas the placebo group exhibited a slight decrease of 0.2 kg (SE 0.1, n = 65) resulting in a significant between-group difference of -12.3 kg (95% CI -13.1 to -11.5; n = 156). In the following 52 weeks, the liraglutide group lost an additional 4.1 kg (SE 1.2, n = 71) whereas the control group was almost unchanged with a weight loss of 0.2 kg (SE 1.2, n = 66). Looking at the main outcome of serum urate levels change, the initial intensive diet resulted in a mean decrease of 0.21 mg/dL (90% CI 0.35 to 0.07; n 155) for the entire cohort. In the following year (week 0 to 52) the liraglutide group exhibited a further mean decrease in serum urate of 0.48 mg/dL (SE 0.11, n = 69), whereas the placebo group exhibited a slight decrease in mean serum urate of 0.07 mg/dL (SE 0.12, n = 65) resulting in a significant between-group difference of -0.40 mg/dL (95% CI -0.69 to -0.12; n 134) – see Figure 1. Four participants in each group experienced serious adverse events; no deaths were observed.

**Conclusion:** This secondary analysis of the LOSE-IT trial suggests that liraglutide provides a potential novel serum urate lowering drug mechanism in obese patient populations, with potential implication for gout treatment.