



Conference Report

# The 16th European Crystal Network (ECN) Workshop—2025 ECN Abstract Proceedings

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## Abstract

**For the 16th Anniversary this year**, the ECN workshop is again held in downtown Paris. Every year the ECN workshop offers **a unique opportunity for clinicians and researchers** interested in crystals, inflammation, and crystal-induced diseases, including gout, **to present their latest results and discuss novel concepts**.

**Keywords:** European Crystal Network; gout; CPPD; urate; hyperuricemia; colchicine; urate transporter

## 1. Introduction

This year we maintained our usual two-day face-to-face meeting schedule with more than 100 colleagues, including dozens of young investigators, from all over the world. Indeed, attendees came from Europe, the USA, and Asia.

We give thanks to the Institut du Cerveau et du Muscle (ICM) for providing a pleasant and comfortable auditorium.

Thanks to the Scientific Committee, we have received 40 abstracts this year and have selected 22 oral communications and 18 posters, which were presented in two sessions.

Again, this year we have the chance, thanks to our twin US G-CAN group, to report these abstracts in this issue of the GUCDD, as was the case for the last two years [1,2]. Only abstracts with permission from their first and/or senior authors are presented herein. All oral communications and lectures have been recorded and are available online with accreditation.

Among 22 oral communications, the two highest-rated abstracts were named as winners of the **2025 ECN Prize**. The Winners were as follows:

1. Riku Takei (Figure 1a);
2. Brenda Kischkel (Figure 1b).



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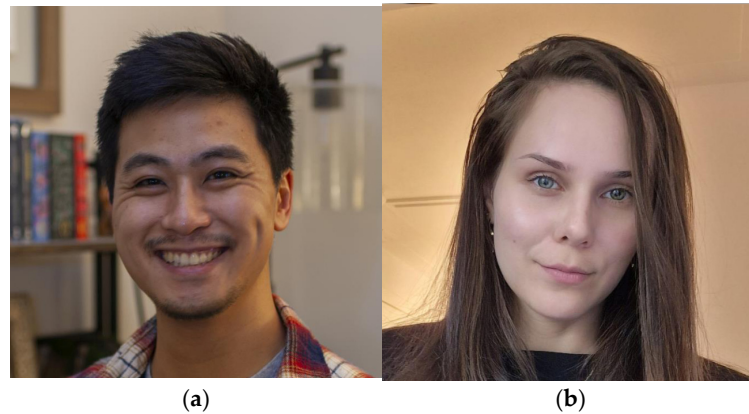
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**Figure 1.** (a) Riku Takei and (b) Brenda Kischkel—winners of the 2025 ECN Prize.

On Thursday, **Riku Takei**, Researcher at the University Of Alabama At Birmingham (UAB), Birmingham, AL, US, presented a brilliant original genetic study on CPP disease, namely, “Genome-wide association study in chondrocalcinosis reveals ENPP1 as a candidate therapeutic target in calcium pyrophosphate deposition disease”.

On Friday, **Brenda Kischkel**, Post-doctoral Researcher at Radboudumc, Nijmegen, The Netherlands, reported on the study “Biomarker found in plasma has potential to differentiate between gout and CPPD disease”.

As the ECN Prize Winners, they will be invited to the 17th ECN Workshop next year.

The 2025 program can be found at: <https://www.european-crystal-network.com/programme>.

We are already preparing the next and 17th ECN workshop in Paris on the 12th and 13th March 2026, at the same venue; save the date and register for updates on the ECN Website to ensure you receive information: <https://www.european-crystal-network.com>.

**2025 Scientific Committee:** Prof. Nathalie Busso (SW), Prof. Dr Jessica Bertrand (GE), Dr Sonia Nasi (SW), Dr Tania Crisan (RO), Prof Michael Doherty (UK), Prof. Leo Joosten (NE), Prof. Robert Terkeltaub (US), Prof. Hyon Choi (US), Prof. Tony Merriman (NZ/US), Prof. Hang-Korng Ea (FR), Dr Hervé Kempf (FR), Prof. Tristan Pascart (FR), Prof. Alexander So (SW), Prof. Fernando Perez-Ruiz (SP), and Prof. Frédéric Lioté (FR)

**2025 Organizing Committee:** Véronique Gordin (Médi-Evènement, FR), Prof. Hang-Korng Ea (FR), Prof. Fernando Perez-Ruiz (SP), Prof. Tristan Pascart (FR), and Prof. Frédéric Lioté (FR)

We thank our **2025 Sponsors:** AMGEN Rare Disease, Olatec, and SOBI.

**Acknowledgments:** Véronique Gordin, Medi-Evènement (FR) for organization and logistics, and Jean-Pierre Voisenet (FR) for technical and IT support.

## 2. Effectiveness of Sodium-Glucose Cotransporter Type 2 Inhibitors and Urate-Lowering Agents in Patients with Gout: Data from a Single-Center Specialized Clinic

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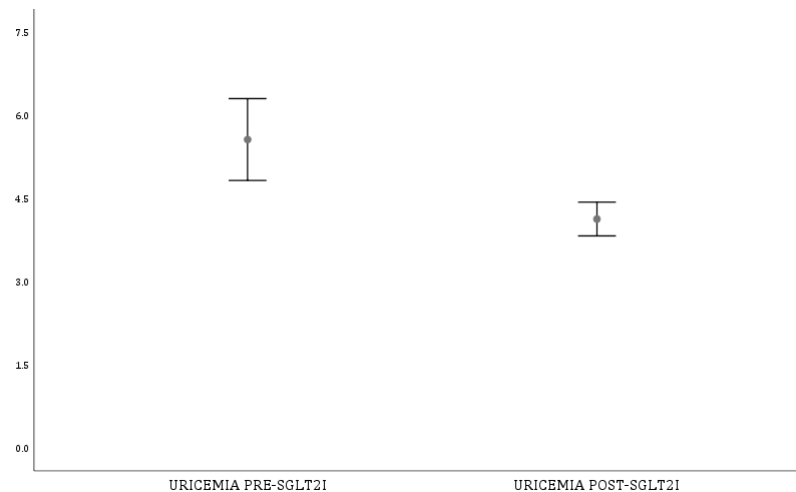
**Abstract:** Background: Sodium-glucose cotransporter type 2 inhibitors (SGLT2Is) have proved substantial benefits in diabetes mellitus (DM), heart failure (HF), and kidney disease (KD). In pivotal trials, SGLT2Is reduced serum urate (SU) levels, but the clinical evidence

in patients with gout under other urate-lowering drugs (ULDs) is scarce [1]. Objectives: To evaluate the urate outcomes in patients with gout treated with SGLT2Is and ULDs in clinical practice. Methods: A retrospective, single-center observational study, enrolling patients with gout from a crystal-arthritis-specialized clinic. We selected those receiving combined treatment with ULDs and SGLT2Is, regardless of the indication. Cases with no serum urate (SU) levels available in the 6 months before and after combined treatment or starting renal replacement therapy were excluded. The main variable of the study was the SU level pre- and post-SGLT2Is (mg/dL), statistically analyzed using the Wilcoxon test as a nonparametric continuous variable. As secondary variables, we measured the percentage achievement of SU target (<6 mg/dL or <5 mg/dL), the required allopurinol dose (mg) and pre-estimated dose according to the Easy-Allo tool (mg) [2]. Other relevant laboratory variables were also collected. Results: Forty-six patients were included; the median age was 76 years (IQR 15.25) and they were 82.6% men, with high comorbidity (91.1% with DM, 58.7% with KD, and 45.7% with HF) and 10 years (IQR 20) of gout duration. As ULD, 66.7% ( $n = 30$ ) of patients were treated with allopurinol, 28.9% ( $n = 13$ ) with febuxostat, and 4.4% ( $n = 2$ ) with benzbromarone. Regarding the SGLT2Is, 58.7% ( $n = 27$ ) received dapagliflozin, 30.4% ( $n = 14$ ) empagliflozin, and 10.9% ( $n = 5$ ) canagliflozin. ULDs were initially prescribed in 81.4% ( $n = 35$ ), while SGLT2Is were prescribed in the remaining 18.6% ( $n = 8$ ). The target of SU <6 mg/dL was achieved in 97.7% (95%CI 88.2–99.6%) of the patients, while 81.4% also reached <5 mg/dL (95%CI 65.5–88.9%). The achievement of the <5 mg/dL target was unrelated to the type of medication prescribed first (ULD 81.3% vs. SGLT2I 87.5%,  $p = 1.000$ ), or the type of xanthine-oxidase inhibitor (allopurinol 79.3% vs. febuxostat 91.7%,  $p = 0.651$ ). The start of SGLT2I treatment showed a median SU reduction of 0.85 mg/dL (IQR 3.02,  $p = 0.001$  for the before–after comparison) (Figure 2). The SU reduction was observed regardless of whether patients were already on ULD (median 0.80, IQR 2.90,  $p = 0.021$ ) or not (median 3.00, IQR 6.95,  $p = 0.018$ ), or of changes in diuretic use ( $p = 0.692$ ). No significant differences in the allopurinol dose were found pre- and post-SGLT2I use but there was a trend towards a lower dosage than pre-estimated by the Easy-Allo tool. The use of SGLT2Is showed significant reductions in fasting glucose, HbA1c, and C-reactive protein levels, increasing urine glucose excretion and creating no differences in urine albumin and glomerular filtration rate. We detected a significant reduction in diuretics use pre- and post-SGLT2Is (60.9% vs. 54.3%,  $p < 0.001$ ). Conclusions: The combination of SGLT2Is and ULDs in patients with gout in clinical practice achieved significant SU level reductions and targets of SU <6 mg/dL and <5 mg/dL. A trend towards a lower dosage requirement of allopurinol was noted, along with a reduced use of diuretics. These promising results require confirmation by further intervention studies.

**Keywords:** observational studies/registry; outcome measures

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**Figure 2.** SU reduction in mg/dL after the start of SGLT2Is (95% Cis present in brackets).

### 3. Telomere Length in Gout and Hyperuricemia: Analysis of Variability and Association with Mononuclear Cell Cytokine Production

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**Abstract:** Introduction: Gout is an inflammatory condition with a high prevalence. It is characterized by recurrent flares driven by monosodium urate (MSU) crystals, which activate the NLRP3 inflammasome and induce the release of pro-inflammatory cytokines such as IL-1 $\beta$  or IL-6. Telomeres are repetitive DNA sequences at the ends of chromosomes and their main function is to prevent the loss of important genetic information during cell division. Telomere length (TL) is a key biomarker of biological aging and has been implicated in various chronic diseases, including gout. Hyperuricemia, the main risk factor for gout, is associated with increased production of reactive oxygen species (ROS), which damage DNA and accelerate telomere shortening. Moreover, the persistent inflammation observed in gout accelerates oxidative stress, a major driver of telomere attrition. Here, we investigate whether telomere length differs among gout patients, hyperuricemic controls, and normouricemic controls. We also examined whether telomere length correlates with the cytokine production capacity of mononuclear cells, as higher levels of pro-inflammatory cytokines may be linked to shorter TL in immune cells. Materials and Methods: The study was performed in the HINT study groups (patients with gout  $n = 81$ , hyperuricemia  $n = 73$  and normouricemic controls  $n = 76$ , Romania). Genomic DNA was isolated from whole blood and average telomere length was determined using the Absolute Human Telomere Length Quantification qPCR Assay Kit (ScienCell, Carlsbad, CA, USA) following the supplier's instructions. Ex vivo functional assays were performed, consisting of PBMC stimulations with C16+MSU (TLR2/NLRP3 inflammasome activator) or LPS (TLR4 ligand) for 24 h. Cytokines were assessed by ELISA. Results: No significant differences in TL were observed between the groups. When stratifying the analysis by distinct age groups, variations in TL were detected, yet no overall correlation was found

between TL serum urate levels or BMI in any of the examined cohorts. Furthermore, no association was identified between TL and the pro-inflammatory cytokine IL-1 $\beta$  or the anti-inflammatory IL-1Ra production of peripheral blood mononuclear cells (PBMCs) in the presence of different stimuli. Conclusions: Our findings suggest that telomere length does not significantly differ between gout patients, hyperuricemic controls, or normouricemic controls, nor does it correlate with serum urate levels, BMI, or pro-inflammatory cytokine production. Given the relatively small study group sizes assessed so far and the complexity of telomere dynamics with inter-individual variability, larger cohorts may be required to detect potential associations and fully elucidate the role of telomere length in gout and hyperuricemia inflammation.

**Keywords:** gout; telomere length; urate; cytokine

#### 4. Colchicine Efficacy and Safety in Crystal-Induced Arthritis Flare in Patients with Severe Chronic Kidney Disease

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**Abstract:** Background: Colchicine is a pivotal treatment recommended for the management of crystal-induced arthritis flares (gout and calcium pyrophosphate deposition (CPPD) disease), but comorbidities associated with these conditions could lead to difficulties in the use of this treatment. Chronic kidney disease (CKD) is regularly associated with these conditions [1], with a five-fold increase in the prevalence of gout in patients with an estimated glomerular filtration rate (eGFR) of <60 mL/min per 1.73 m<sup>2</sup> when compared with patients without kidney disease [2]. As colchicine is excreted by the kidneys and minimally removed by dialysis, treating acute flares in patients with CKD can be challenging. Nevertheless, colchicine is commonly used in clinical practice in patients with severe CKD (eGFR < 30 mL/min per 1.73 m<sup>2</sup>), where potential toxicity is enhanced. Objectives: To analyze the prescription of colchicine and its efficacy and safety in the management of crystal-induced arthritis flares in patients with severe CKD. Methods: All crystal-induced arthritis flares (gout or CPPD disease) treated by colchicine in hospitalized patients with severe CKD or on dialysis in four French centers were screened from January 2015 to December 2023. Data were collected retrospectively from medical records. Treatment efficacy was assessed by a composite criterion including clinical improvement estimated by the medical team by decrease in C-reactive protein levels as compared with the level prior to starting treatment. Results: Out of 159 hospitalizations, 157 patients (101 men; median age: 80 years; IQR 71–88) with colchicine prescriptions were screened. Among them, the prescriptions concerned 141 cases of gout flares and 18 cases of CPPD disease arthritis. The median eGFR was 23 mL/min per 1.73 m<sup>2</sup> (IQR 18–25), with 133 patients with stage 4 CKD

and 26 patients with stage 5 CKD, including 21 on dialysis and 13 who had undergone kidney transplantation. The main reasons for hospitalization were joint pain (24%), heart failure (18%), and fall (8%). Initial colchicine dosage was 0.5 mg/day in 86 cases (54%), with no dosage exceeding 1 mg/day, except for one patient who received 1.5 mg per day. The median duration of treatment was ten days (IQR 7–14). Colchicine was considered effective in 145 cases (91%), with dosage adaptation not required in most situations. Concerning tolerance, three cases of acute renal function deterioration, one colchicine-induced hepatitis, and three overdosages of a vitamin K antagonist without bleeding complications were reported. Conclusion: This real-life study concerning use of colchicine for crystal-induced arthritis flares in patients with severe CKD provides reassuring data. Considering dose reduction, colchicine could be used in these conditions with caution and close monitoring.

**Keywords:** colchicine; gout; CPPD; chronic kidney disease

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## 5. Learning from GoutSMART: Predicting Time to Cessation of Gout Flares

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**Abstract:** Background: Lower urate levels are associated with reduced flare frequency in gout, with a treat-to-target urate approach showing reduction in flares by year two of treatment [1]. There are insufficient long-term studies of gout to allow the time to final gout flare to be predicted with confidence. Objective: To assess predictors at baseline of time to a final gout flare. Status: This is an exploratory analysis of data from previously completed trials. Methodology: We have developed a smartphone app (GoutSMART) which encourages patients to maintain a diary of gout flares and urate levels. A randomized controlled feasibility trial in 60 patients showed that use of the GoutSMART app over one year helped patients achieve urate targets and a reduction in gout flares superior to usual care [2]. Furthermore, a two-year extension of the GoutSMART trial has demonstrated that continued two-monthly urate monitoring results in cessation of flares in most participants [3]. Flares were adjudicated using criteria published by Gaffo et al. [4]. A regression analysis was performed in participants who reached the end of the extension trial with >12 months flare-free, investigating the number of days to last flare. To calculate the number of days to final flare, we calculated the difference between the trial start date of a participant and the date of their final flare. Those participants who did not have a flare since the start date of their trial (i.e., the number of days to last flare was 0) were included in the regression analysis. Findings: By the end of the two years, 28 (93.3%) of 30 active care participants were flare-free compared to 8 (72.7%) of 11 under usual care ( $p = 0.052$ ). The average number of days to final flare in the 36 flare-free participants was 259.64 (SD = 229.24). In a multiple linear regression analysis that included the number of baseline flares, BMI, age, urate level, number of comorbidities, presence of tophi, colchicine prophylaxis, and sex, the only significant factors predicting the number of days to last flare were the number

of baseline flares ( $p < 0.01$ ) and colchicine prophylaxis ( $p < 0.05$ ). In a univariate analysis, the average days to last flare in participants having  $\leq 3$  flares a year at baseline was 189, compared to 472 days in those having  $\geq 4$  flares ( $p < 0.001$ ). A linear model predicted the number of days to final flare is 87 days multiplied by the number of baseline flares, with an added 33 days. The average number of days to final flare in patients who were on colchicine prophylaxis was 193 (SD = 168), compared to 282 (SD = 245) for those not on colchicine prophylaxis. However, this was not significant when considering these two variables alone ( $p = 0.319$ ). Significance: Stratification of patients by the number of flares sustained in the last year leads to more than doubling of the estimated time to cessation of flares. This analysis should help patients make informed decisions around when to start urate-lowering therapy. Further research in a larger number of patients is needed to fully determine clinical predictors of the time to final flare and investigate the role of colchicine prophylaxis in the time to final flare.

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## 6. Comorbidity Burden and Health Resource Utilization in Controlled Vs. Uncontrolled Gout: A Retrospective Claims-Based Analysis

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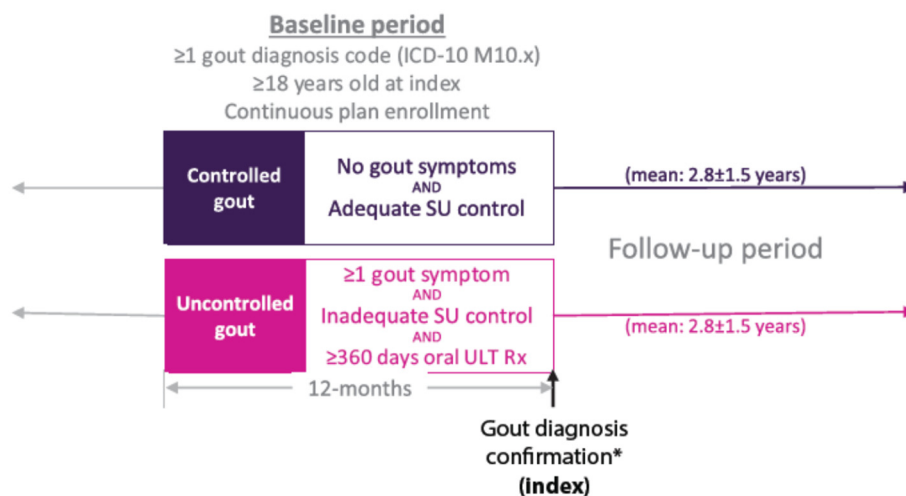
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**Abstract:** Introduction: Compared to patients (pts) without gout, pts with gout have higher comorbidity [1], health resource utilization (HRU) [2], and mortality (cardiovascular [3] and all-cause [4]). Quality of life is also impacted, particularly by pain and gout flares [5]. A prior study showed higher comorbidity burdens in pts with uncontrolled vs. controlled gout, including increased CKD and cardiovascular disease (CVD) prevalence [6]. Here, we further explore comorbidities and HRU in pts with uncontrolled vs. controlled gout. Methods: Closed-claims data were examined (2015–2023; Merative™ MarketScan® Research Databases, commercially insured (primary and secondary plans)). Date of gout diagnosis confirmation was set as index (Figure 3). Inclusion criteria were an age of  $\geq 18$  years at index and the presence of a gout diagnosis code (ICD-10 M10.\*) during the baseline period (one year prior to index). Controlled pts had no gout symptoms (tophi, flare, or

gout-related ED/hospital visit) during baseline and a last pre-index serum urate (SU) <6 mg/dL. Uncontrolled pts had gout symptoms during baseline, elevated SU (last pre-index  $\geq 8$  mg/dL or pre-index  $\geq 6$  mg/dL for  $\geq 3$  months), and  $\geq 360$  days oral ULT use. CVD was identified as any Disease of the Circulatory System (100–199, including hypertension), CKD as unspecified/staged CKD (N18.\*), and gout-related pain as joint pain (M25.5\*) or joint aspiration (20,600, 4–6, 10, 11). Gout-related HRU encounters had an associated gout code (in any position). Results: 2435 uncontrolled (83% men, age:  $56.8 \pm 13.4$  years, with baseline SU:  $8.5 \pm 1.7$  mg/dL) and 2697 controlled (81% men, age:  $60.5 \pm 12.5$  yrs, with baseline SU:  $5.1 \pm 1.2$  mg/dL) pts were included. Stage 3–5 CKD (28% vs. 18%), cardiac events (11% vs. 6%), ischemic heart disease (IHD; 21% vs. 15%), and VTE (4% vs. 2%) had significantly higher prevalence during baseline despite the younger age of uncontrolled gout pts (all  $p < 0.001$ ). Uncontrolled pts also had higher rates of gout-related pain (48% vs. 23%) and anxiety (9% vs. 7%, both  $p < 0.001$ ). After gout diagnosis confirmation, incidence of nonfatal stroke, IHD, and heart failure were significantly higher in uncontrolled vs. controlled pts (both pts in database  $2.8 \pm 1.5$  yrs after index, all  $p < 0.001$ ). Uncontrolled gout pts also had more CKD development/worsening (based on highest CKD stage) and higher HRU, including all-cause and gout-related hospitalization, ED visits, and urgent care visits. Conclusion: Though causality cannot be established, these findings strongly suggest higher disease burden and progression in pts with uncontrolled vs. controlled gout. It is of note that the differences in controlled gout pts were noted within the first few years after gout diagnosis, with uncontrolled gout pts having a higher incidence of stroke, ICD, and heart failure, more CKD development/progression, and higher HRU.



**Figure 3.** Patient selection criteria and controlled/uncontrolled gout classification. \* Date of first tophi code, first gout-related ED/inpatient visit, or second flare. Gout symptoms are defined as tophi, flare, or gout-related emergency department/inpatient visit. Adequate SU control is defined as a last baseline SU <6 mg/dL. Inadequate SU control is defined as a last baseline SU  $\geq 8$  mg/dL or a SU  $\geq 6$  mg/dL for  $\geq 3$  months during the baseline period. SU: serum urate level; ULT: urate-lowering therapy; Rx: prescription.

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## 7. Transmembrane Proteins TMEM171 and TMEM174: Two Novel Physiological Regulators of Urate Homeostasis

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**Abstract:** Early genome-wide association studies (GWAS) identified *TMEM171* (transmembrane protein 171) as a genetic determinant of SUA variation and the risk of gout. The causal genetic variant, *rs17632159*, is in fact intergenic, mapping between *TMEM171* and the adjacent *TMEM174* gene. We demonstrate here that the *TMEM171* and *TMEM174* proteins are novel physiological regulators of urate transport. Immunohistochemistry of the human kidney indicates that the *TMEM17* protein is found in the basolateral membrane and the cytoplasm of proximal and distal tubule cells, whereas the *TMEM174* protein is selectively expressed at the apical membrane of proximal-tubule cells. *TMEM171* and *TMEM174*, expressed in transfected HEK 293T cells or *Xenopus* oocytes, did not show urate transport activity. However, both proteins efficiently inhibited the urate transport activities of URAT1, OAT10, OAT1, OAT3, ABCG2 and ABCC4 and inhibited the N-glycosylation of GLUT9 isoform proteins, without affecting the N-glycosylation of URAT1 or OAT10. Both the *TMEM171* and *TMEM174* proteins co-immunoprecipitate with GLUT9 isoforms. However, unlike *TMEM174*, *TMEM171* efficiently inhibits the urate transport activities of GLUT9 isoforms and of GLUT9 N-glycosylation-deficient mutants, indicating that the inhibitory effect of *TMEM171* is independent on its inhibitory effects on glycosylation. The urate-increasing gout risk allele (G) at *rs17632159* is associated with lower expression of *TMEM171* in esophagus mucosa in the Genotype-Tissue Expression Database ( $p = 1.9 \times 10^{-5}$ ). We also leveraged kidney expression quantitative trait locus (eQTL) data and found that *rs17632159* was the lead associated SNP associated with *TMEM171* expression in kidney tubules; again, the G-allele was also associated with lower renal tubular expression of *TMEM171*. Notably, *rs17632159* is within the core motif of a predicted binding site for the CTCF transcription

factor, and maps to a genomic location with enhancer histone marks in nine tissues, along with five bound transcription factor proteins (CTCF, RAD21, SMC3, ZNF263, and NR2F1). We tested the 818 bp segment of DNA containing *rs17632159* for enhancer activity in human cell-based and zebrafish assays. We found significant enhancer activity of a construct containing the C-allele in HEK293 cells, consistent with this allele being associated with higher expression of *TMEM171* in the kidney tubule. In summary, we report that the *TMEM171* and *TMEM174* “digenic” locus is a novel regulator of urate homeostasis, through effects of both proteins on urate transporter activity. In particular, *TMEM171* is a potent inhibitor of GLUT9-mediated urate transport. The causal *rs17632159* variant appears to selectively affect transcriptional regulation of the *TMEM171* gene, with the urate-decreasing allele increasing expression of *TMEM171* and thus amplifying the inhibitory effect of *TMEM171* on GLUT9 function and proximal tubular urate reabsorption.

## 8. Urate Transport Mediated by SLC23A Proteins That Are Known as Vitamin C Transporters

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**Abstract:** Uric acid, the end product of purine metabolism in humans, is a significant substance because of its anti-oxidant activity and causal relationship with hyperuricemia and gout. Like vitamin C (VC), another water-soluble anti-oxidant known as ascorbic acid, uric acid mainly exists as its anion form (urate) under physiological conditions; therefore, it cannot passively penetrate the plasma membrane, highlighting the fact that active transport plays a pivotal role in regulating urate handling in humans. Indeed, several physiologically important urate transporters regulate this water-soluble metabolite in our body; however, previously identified urate transporters do not thoroughly explain such handling systems, suggesting the presence of latent machineries. To address this issue, herein, we focused on SLC23A proteins that have been identified as sodium-dependent vitamin C transporters (SVCTs) given the following: (1) we previously identified SLC2A12 as a physiologically important urate and VC transporter (PNAS, 2020 [1]; iScience, 2022 [2]); (2) a homology search revealed that SLC23A1/SVCT1 and SLC23A2/SVCT2 are the closest to YgfU, a urate transporter in *E. coli* which belongs to the nucleobase-ascorbate transporter (NAT) family, in amino acid sequence; (3) only SLC23A proteins are members of the NAT family in humans. To examine whether SVCT1 and SVCT2 transport urate, we conducted cell-based analyses using transporter-expressing mammalian cells for each. The results demonstrated that SVCT1 [1] and SVCT2 [2] are novel urate transporters characterized by their lower affinity for urate compared with already-identified urate importers. Similar results were obtained for mouse *Svct1* and *Svct2*. Regarding SVCT1, we generated *Svct1* knockout (KO) mice lacking both *urate transporter 1* and *uricase*. In this hyperuricemic model, serum urate concentrations were lower than controls, suggesting that *Svct1* disruption could reduce serum urate [3]. As *Svct1* serves as a renal vitamin C re-absorber, it could also be involved in the reabsorption of urate in the kidney. Regarding SVCT2, focusing on its molecular properties as a sodium-dependent urate importer, we established a convenient mammalian cell-based urate efflux assay using SVCT2-expressing cells for urate exporter hunting [4]. Additionally, VC inhibited the urate transport activity of SVCT2 with a half-maximal inhibitory concentration of 36.59  $\mu\text{M}$ , suggesting that the SVCT2-mediated urate transport may be sensitive to physiological ascorbate levels in blood. However, the physiological role of SVCT2 as a urate transporter remains to be investigated; because *Svct2* knockout mice die

soon after birth, a conditional knockout approach will be required for investigation. While further studies are required to obtain deeper insights into the underlying mechanisms, our findings regarding the dual-substrate specificity of SVCT1 and SVCT2 expand the understanding of handling systems for the water-soluble antioxidants in our body as well as the functional evolutionary changes in NAT family proteins.

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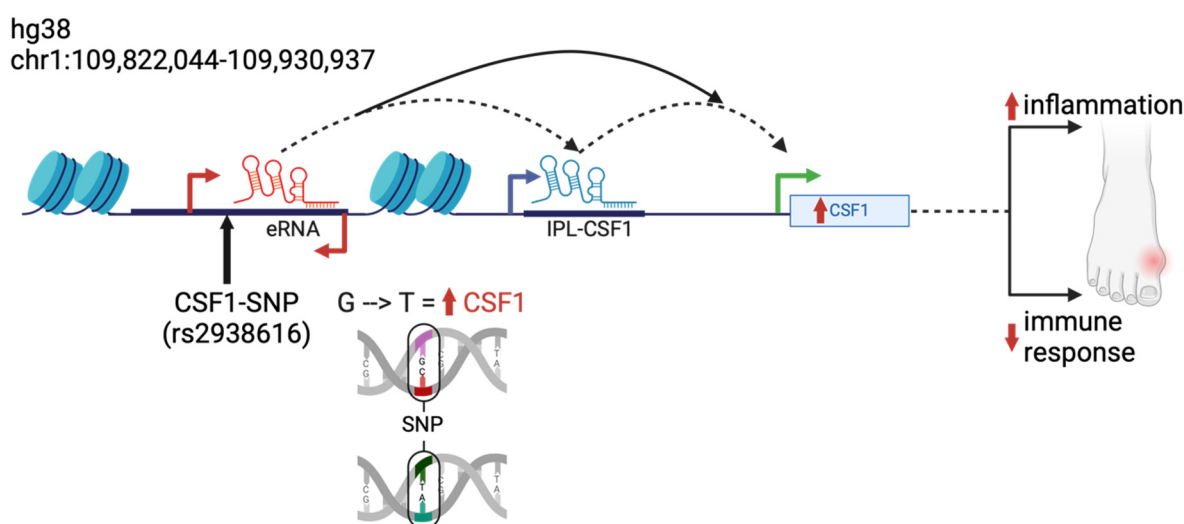
### 9. Identification of Non-Coding RNAs Controlling Gout-Relevant Genes

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**Abstract:** Background: Gout is characterized by flares caused by monosodium urate (MSU) crystal deposition and subsequent activation of innate immune cells. A recent genome-wide association study (GWAS) identified many gout-associated variants that may affect genes related to this immune response. It is important to translate these genetic associations into mechanistic and molecular insights for new druggable targets to prevent gout flares. Hereby, we focus on the non-coding RNAs (ncRNAs) controlling the transcription levels of putative gout flare-related genes (Figure 4) that are not associated with hyperuricemia. This includes the previously unknown CSF1-CSF1R axis in gout. Objectives: In this study, we aimed to investigate a potential immune gene-priming long non-coding RNA (IPL) and an enhancer RNA (eRNA) of colony-stimulating factor 1 (CSF1) and assessed its role in gouty arthritis. Methods: Characterization was performed on the transcription levels (IPL, eRNA,

and mRNA) in a controlled and stimulated setup to validate the presence of these RNAs and their effects on CSF1 concentrations. Initial experiments were performed in THP-1 cells to establish the technology needed for the extraordinarily low-expressed RNAs. Based on the GWAS hits, we focused on validating IPL, eRNA, and CSF1-mRNA in qPCR and dPCR experiments. Furthermore, the Olink proximity extension assay was used to determine CSF1 plasma concentrations in gout patients within a flare or the inter-critical phase. Findings: In order to specifically study CSF1, as well as its potential regulatory ncRNAs, we designed an experimental setup upregulating CSF1 expression. Initial experiments were carried out with 4 to 96 h PMA-stimulated THP-1 cells, since they had higher availability and higher RNA concentrations. This allowed us to verify the upregulation of CSF1 and CSF1R by PMA and the link between the eRNA and IPL transcription. Whereas CSF1 and CSF1R show a continuous increase over the time course, the ncRNAs suggest an initial peak after 4h stimulation, thus suggesting a different order of activation by PMA. Future experiments will be focused on primary human monocytes of gout patients, resembling in vivo settings. Significance: This study improves the understanding of the transition from hyperuricemia to gout by focusing on gout-associated genes that do not appear to play a role in hyperuricemia. Furthermore, unraveling the molecular pathways will improve therapeutic interventions by providing novel targets for gout.



**Figure 4.** Schematic overview of CSF1, its potential ncRNAs, and its regulatory functions in gout. The SNP (rs2938616, exchange of G to T) causes an upregulation of CSF1 transcription in the context of gout. The closely located ncRNAs, eRNA and IPL-CSF1, are potentially involved in this regulatory process, demonstrated by the arrows above the genes. The dual role of CSF1, having pro- and anti-inflammatory properties, allows no obvious interpretation for gouty arthritis.

## 10. Serum Metabolomics Reveals Dyslipidaemia in Gout and Hyperuricemia: Exploring Inflammatory Links Through Integrative Multi-Omics

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**Abstract:** Background and Objectives: Gout and asymptomatic hyperuricemia (AH) are characterized by both metabolic dysregulation and systemic inflammation, yet the interplay between lipid alterations and inflammatory responses remains insufficiently understood. Nuclear magnetic resonance (NMR)-based metabolomics enables the characterization of metabolite and lipid species, providing insights into the metabolic disturbances associated with these conditions. While dyslipidaemia, including elevated very-low-density lipoprotein (VLDL), has been previously reported in gout and AH, its relationship with inflammatory pathways remains unclear. This study aims to: (i) identify metabolomic and lipidomic alterations distinguishing gout and AH from normouricemic controls; (ii) investigate the correlations between these metabolic shifts and *in vivo* inflammatory responses; (iii) explore potential mechanistic links *in vitro* through peripheral blood mononuclear cell (PBMC) stimulations. Methods: Serum samples from patients with gout, AH, and normouricemic control patients were analyzed using an NMR-targeted metabolomics approach to profile lipid and metabolic alterations. Principal component analysis (PCA) and partial least squares discriminant analysis (PLS-DA) were employed to identify key metabolites differentiating groups, while correlation analyses with inflammatory serum proteins provided insights into lipid-associated immune activation. Results: Preliminary analyses reveal a distinct lipidomic profile in gout and AH, characterized by alterations in multiple lipid species, including VLDL-related fractions and other lipoprotein-associated metabolites. These metabolic changes show correlations with inflammatory serum proteins, suggesting a potential interaction between dyslipidemia and immune activation. Conclusions and Significance: This study integrates targeted metabolomics and proteomics to examine metabolic–inflammatory interactions in gout and AH. By integrating NMR-based metabolic profiling with inflammatory protein signatures *in vivo* and further functional immune responses *in vitro*, we demonstrate that dyslipidemia may play a role in immune activation, potentially informing metabolic and immunomodulatory therapeutic strategies. Future studies will extend these findings by conducting *in vitro* PBMC stimulations with soluble urate and Toll-like receptor (TLR) ligands to assess cytokine production (IL-1 $\beta$ , IL-1Ra, and IL-6) in relation to observed lipidomic alterations. Additionally, VLDL stimulations will be explored to determine its inflammatory potential, providing mechanistic insights into its contribution to systemic inflammation in gout and AH. These ongoing investigations aim to determine whether targeting lipid alterations could offer novel avenues for reducing inflammation in hyperuricemic conditions.

## 11. Gout Characteristics, Comorbidities and Management in a Long Primary Care Database from Catalonia: The GotAP Study

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**Abstract:** Background: Although gout treatment is well established, its management has been proven to be insufficient in all healthcare settings, with clinical treatment differences between regions. Objective: To describe demographic, disease, and treatment characteristics in a cohort of incident gout patients over the last decade. Methods: A retrospective cohort study using a primary-care database (SIDIAP) with routinely collected medical records and pharmacy dispensations covering more than 75% of the population of Catalonia, Spain (~6 million people). People with an incident of gout diagnosis were included and followed from 2012 to 2023. Sociodemographic features, medications adherence (Medication Possession Ratio (MPR) > 80% was considered a good adherence) and uric acid levels (more than 80% of the time in the study with target uric acid was considered good

control) were collected. Results: 97,239 people were included. Median follow up was 5.4 [2.5; 8.2] years. A total of 79.9% of patients were male, with a mean age of  $66.3 \pm 14.6$  years and a mean BMI of  $30.1 \pm 5.0$  kg/m<sup>2</sup>. Uric acid level previous to the diagnosis of gout was 8.00 [6.90; 9.00] mg/dL. At gout diagnosis, 65.3% had hypertension, 50.9% dyslipidaemia, 24.3% diabetes mellitus 2, 11.1% ischemic heart disease, 6.8% cerebrovascular disease, 32.9% stage III to V chronic kidney disease (CKD), and 4.6% alcohol abuse. During the follow-up, uric acid levels were never measured in 11.2% of the patients and 37.0% never received urate lowering therapy (ULT). Initial ULTs were alopurinol (94.9%), febuxostat (5.0%), and benzbromarone (0.05%). When analyzing the final ULT, patients treated with febuxostat were younger (70.6 vs. 72.4 years old), had longer treatment periods (2.6 vs. 3.3 years) and had a higher incidence of CKD (56.5 vs. 42.0%) compared to alopurinol patients. Patients with ischemic heart disease were more frequently treated with alopurinol (14.4 vs. 12.3%). Treatment adherence was greater among febuxostat patients (50.3% vs. 5.7%). Mean duration of alopurinol was 111.5 [25; 208] days, whereas for febuxostat it was 179 days [56; 546]. In 25% of the patients ULT treatment did not arrive to 25 days. The first ULT treatment was initiated 1.8 [0.5; 8.5] months after the gout diagnosis and its duration was 3.72 [0.8; 9.8] months. The prevalence and incidence of ULTs during the study and the differences between male and female patients are shown in Figure 5. A total of 12.4% of the patients achieved good control. The likelihood of good control did not change according to the number of uric levels tests performed, the year of diagnosis or the time of the follow-up. Characteristics associated with good control were as follows: the time under ULT, the alopurinol dose (100 vs. 212.5 mg/day), MPR, treatment with febuxostat, cerebrovascular disease and diabetes mellitus. Characteristics contraindicating good gout control were as follows: being male, extended time to the beginning of ULT, a higher BMI, CKD III-IV, dyslipidaemia, hypertension, alcohol abuse, and Charlson Index. The association between adherence and good control is shown in Figure 6. Prevalence and incidence of good control during the study and the differences between male and female patients are shown in Figure 4. Conclusions: The majority of patients have cardiovascular comorbidities. Most of the patients are undertreated and have a poor adherence to ULT. Being a female, starting ULT after diagnosis, using febuxostat, using high doses of alopurinol, and having a greater MPR is associated with better control of gout. Women were less treated than men but had better outcomes. Management of gout has not improved during the last decade.

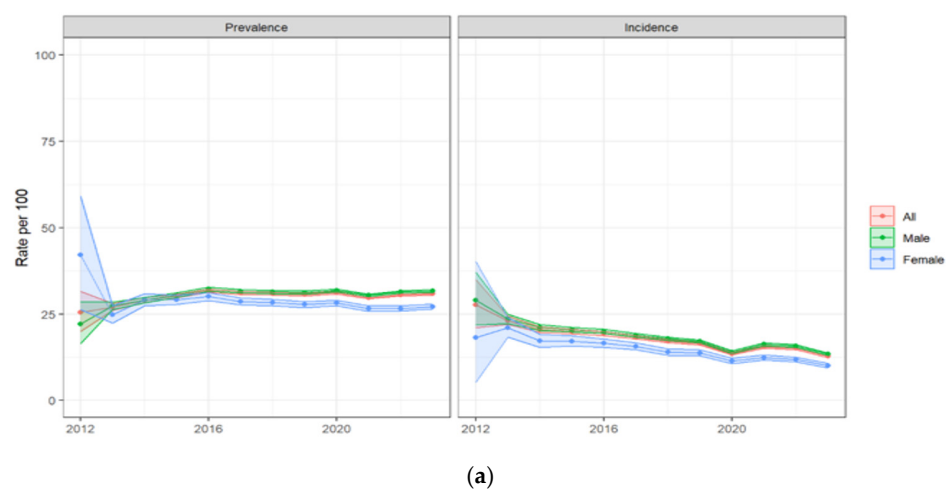
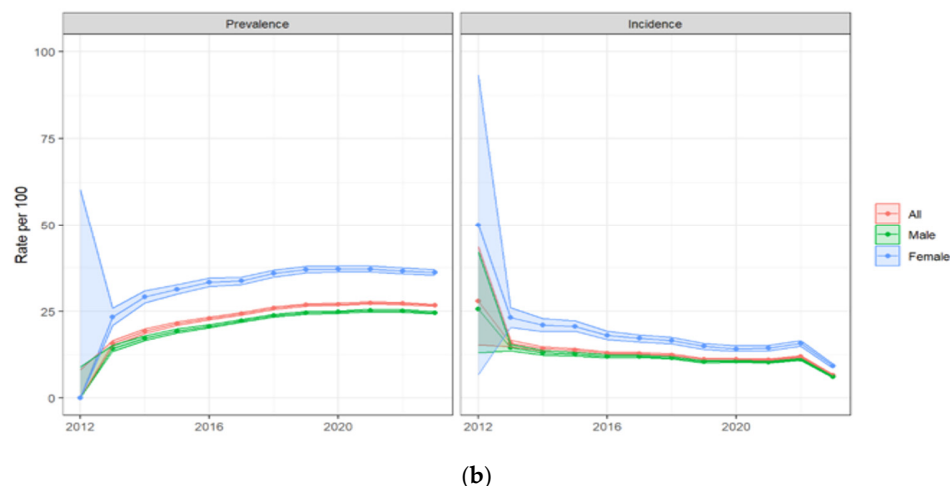
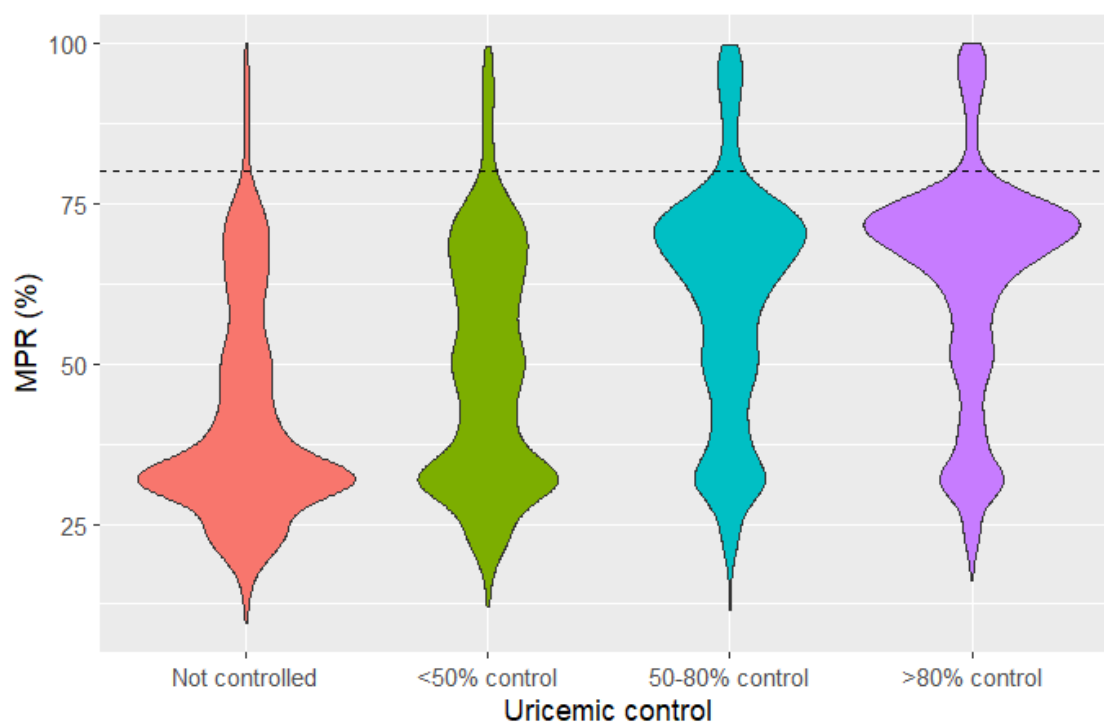


Figure 5. Cont.



**Figure 5.** (a) Prevalence and incidence rate per 100 patients (CI95%) of urate lowering therapy and (b) prevalence and incidence of good control patients.



**Figure 6.** Distribution of the MPR (%) values as a function of uricemic control, for patients with a high percentage of time under treatment. The dashed line represents the value at which a good response is defined.

## 12. Interleukin-40 in Hyperuricemia and Gout

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**Abstract:** Background: IL-40 is a recently described pro-inflammatory cytokine and its role and significance in the pathogenesis of gout has not yet been described. Objectives:

Our aim was to determine the level of IL-40 in the serum of patients with hyperuricemia and/or gout as well as to conduct a genetic analysis of the gene encoding IL-40 (C17orf99 gene). Methods: The study cohort collected in the Bank of Biological Materials of Institute of Rheumatology included a control group of 48 subjects with no history of primary hyperuricemia/gout, 54 patients with asymptomatic hyperuricemia, 156 patients with intercritical gout, 25 patients with chronic tophaceous gout, 12 patients with acute gouty flares, and 84 pediatric hyperuricemia patients. Asymptomatic hyperuricemic patients were classified as having serum uric acid (SUA) > 420  $\mu\text{mol/L}$  for men and SUA > 360  $\mu\text{mol/L}$  for women. Gout patients met the 1977 American Rheumatism Association preliminary classification criteria for acute arthritis of primary gout. Plasma IL-40 was analyzed using enzyme-linked immunosorbent assay. The coding regions and intron-exon boundaries of C17orf99 gene were analyzed by Sanger sequencing. Results: Serum IL-40 levels were significantly lower in the control group compared to in the group of asymptomatic hyperuricemia patients ( $p < 0.0001$ ), patients with gout ( $p < 0.0001$ ), patients during acute gout flare ( $p = 0.0001$ ) and in chronic tophaceous gout patients ( $p = 0.0023$ ). Significantly higher levels were also observed in pediatric patients with hyperuricemia or gout ( $p < 0.0001$ ). Levels of IL-40 in serum have a slight downward trend with later onset of disease independent of the group: the higher the age of onset, the lower the measured IL-40 value ( $p = 0.005$ ); an estimated decrease of 0.91 times (95%CI 0.85–0.97) per 10 years of later onset. Levels of IL-40 in serum were higher among those with higher CRP ( $p < 0.001$ ) and serum uric acid (off treatment,  $p < 0.001$ ) levels, independent of the group. Three intron and one allelic exon genetic variant of IL-40 were identified and their associations with the clinical variants of hyperuricemia and gout were evaluated. Conclusions: We demonstrated the up-regulation of IL-40 levels across the clinical phases of gout: asymptomatic hyperuricemia, intercritical, and chronic tophaceous gout compared to controls and its association with systemic inflammation, uric acid levels, and disease onset. Funded by: Ministry of Health (MH), Czech Republic (CZ), NU22-01-00465, and BBMRICZ LM2023033.

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