



Conference Report

Gout, Hyperuricemia and Crystal-Associated Disease Network (G-CAN) Conference 2023: Early-Career Investigators' Abstracts

Gout, Hyperuricemia and Crystal-Associated Disease Network

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Abstract: The ninth annual international G-CAN research symposium was held in La Jolla, CA on the 7th and 8th of November 2023. This hybrid meeting, a live face-to-face and virtual live symposium, was attended by 191 participants. Over 20 research abstract submissions were received from early-career investigators, for plenary oral and poster presentations. Here, we present the 20 accepted, lightly edited abstracts from the early-career presenters consenting to have their materials published. We thank and congratulate the presenters for their work and contributions to the meeting.

Keywords: gout; urate; crystal; CPPD; BCP

1. Interleukin 1 Receptor Type I and II Variation in Patients with Gout and Hyperuricemic Individuals

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Abstract: Background: Gout is an important inflammatory disease with high prevalence in developed countries. Necessary for developing gout is the deposition of monosodium urate (MSU) crystals in the joint and other tissues as a result of elevated serum urate levels. Interleukin IL-1 β is the central inflammatory cytokine in gout, and its effects are mediated through signaling via IL1 receptor type I (IL1R1). The IL1 receptor type II (IL1R2) is a defective receptor that functions as a decoy and antagonizes IL-1 β signaling. *IL1R1* is a newly identified locus associated with gout in a recent GWAS and is a candidate gene for a role in the progression from hyperuricemia to gout. Differential expression of the *IL1R1* gene was previously reported in monocytes exposed to lipopolysaccharide or MSU crystals. Here, we further assessed *IL1R1* (and neighboring *IL1R2*) expression in gout and hyperuricemia. We also assessed the gout-associated *IL1R1* rs17767183 variant for association with the cytokine production capacity of mononuclear cells. Methods: The study was performed in the HINT study groups (patients with gout and controls, Romania) and the 500FG (healthy volunteers, The Netherlands). RNA sequencing was used to assess the gene transcription in freshly isolated PBMCs from people with gout or with asymptomatic hyperuricemia or normouricemia. Circulating soluble IL1R1 and



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IL1R2 levels were measured in plasma. Genomic DNA was isolated from whole blood, and genotyping was performed using the Illumina Infinium Global Screening Array. Ex vivo functional assays were performed, consisting of PBMC stimulations with C16 + MSU (TLR2/NLRP3 inflammasome activator) or LPS (TLR4 ligand) for 24h. Cytokines were assessed by ELISA. Results: *IL1R1* and *IL1R2* were differentially expressed in PBMCs from gout patients compared to controls. Serum soluble IL1R1 protein levels were very low, and there were no differences in the studied groups. Plasma soluble IL1R2 concentrations were higher in both gout and hyperuricemia when compared to normouricemia. Moreover, *IL1R1* expression positively correlated with serum urate levels in vivo and with ex vivo cytokine production. The *IL1R1* rs17767183 SNP was not associated with changes in *IL1R1* expression or cytokine production in the HINT study groups. However, the *IL1R1* rs17767183 C (gout risk) allele was associated with significantly elevated IL-6 cytokine production in response to C16 + MSU crystal in 500FG healthy controls. Conclusions: Variation in expression of *IL1R1* and *IL1R2* is observed in primary PBMCs of patients with gout and in hyperuricemic controls thus reinforcing data implicating these loci in gout and urate-related inflammation. *IL1R1* expression positively correlates with in vivo urate levels and responses to several ex vivo stimuli. Discordant results were observed for cytokine production levels in relationship to the *IL1R1* rs17767183 SNP, and further analysis into the possible regulatory effects of this SNP in inflammation is currently ongoing.

2. Dual Energy Computed Tomography (DECT) Urate Volume Predicts Fulfillment of Gout Remission after Two Years of Intensive Urate-Lowering Therapy

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Abstract: Background: Preliminary gout remission criteria have been developed using OMERACT core outcome domains for long-term gout studies. This study aimed to identify variables that predict gout remission in patients receiving intensive urate-lowering therapy. Methods: We analyzed data from a 2-year, double-blind randomized controlled trial of 104 people with erosive gout. Participants were randomized to an intensive serum urate target of <0.20 mmol/L or a standard target of <0.30 mmol/L using oral urate-lowering therapies (allopurinol, febuxostat, probenecid and benzbromarone). All participants had a dual energy CT (DECT) scan of the feet and ankles at baseline. The proportion of participants achieving gout remission according to the preliminary gout remission criteria, and also simplified gout remission criteria without the patient-reported outcomes at Year 1 and Year 2, was calculated (Table 1). The simplified gout remission criteria were developed following a qualitative study examining patient perspectives of gout remission. Logistic regression models were used to evaluate independent predictors of gout remission at Year 2; these included baseline variables associated with remission in bivariate analysis and baseline values for each remission domain. Results: The preliminary gout remission criteria were fulfilled in 11 (11%) of all participants at Year 1 and 21 (23%) of all participants at Year 2. The simplified criteria were fulfilled in 26 (27%) participants at Year 1 and 40 (44%) participants at Year 2. Similar rates of remission were observed in the two randomization groups ($p > 0.99$). In regression models, baseline DECT urate volume was the only significant predictor of gout remission at Year 2 using either criterion. Each 1 cm³ increase in the baseline DECT urate volume decreased the odds of fulfilling the preliminary gout remission criteria with an odds ratio of 0.65 [95% CI 0.44–0.96], $p = 0.029$. Likewise, each

1 cm³ increase in the baseline DECT urate volume decreased the odds of fulfilling the simplified gout remission criteria with an odds ratio of 0.56 [95% CI 0.39–0.77], *p* < 0.001. Conclusions: In people with erosive gout on urate-lowering therapy, high baseline MSU crystal volume measured by DECT is associated with lower odds of gout remission after 2 years of treatment, defined by both the preliminary gout remission criteria and simplified gout remission criteria.

Table 1. Preliminary gout remission criteria [1] and the simplified gout remission criteria used in this analysis.

Preliminary Gout Remission Criteria	Simplified Gout Remission Criteria
Absence of gout flares in the last 12 months	Absence of gout flares in the last 12 months
Absence of tophi	Absence of tophi
Serum urate <0.36 mmol/L measured at least twice in the last 12 months,	Serum urate <0.36 mmol/L measured at least twice in the last 12 months
Pain due to gout <2 at least twice in the last 12 months and no value 2 or more, using a 10-cm visual analogue scale or 10-point Likert scale	
Patient global assessment <2 at least twice in the last 12 months and no value 2 or more, using a 10-cm visual analogue scale or 10-point Likert scale	

[1] de Lautour, H.; Taylor, W.J.; Adebajo, A.; Alten, R.; Burgos-Vargas, R.; Chapman, P.; Cimmino, M.A.; da Rocha Castelar Pinheiro, G.; Day, R.; Harrold, L.R.; et al. Development of Preliminary Remission Criteria for Gout Using Delphi and 1000Minds Consensus Exercises. *Arthritis Care Res. (Hoboken)* **2016**, *68*, 667–672.

3. Automated Classification of Raman Spectra for an Objective Diagnosis of Crystal Arthropathies

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Abstract: Background: Raman spectroscopy has been proposed as a next-generation method for the identification of MSU and CPP crystals in synovial fluid. As the interpretation of Raman spectra requires specific expertise, the method is not that suitable for clinical use. With this project we show that the identification process can be automated with machine learning algorithms. Methods: We collected synovial fluid samples from 247 patients with various rheumatic diseases from VieCuri Medical Centre, Maastricht UMC and UMCG. In each sample, we scanned birefringent crystals with our Raman spectroscope and collected spectral data. Two trained observers (TN, CO) classified every Raman spectrum as MSU, CPP or else. The spectral data were pre-processed to correct for day-to-day variations in the Raman signal. We designed two one-against-all classifiers, one for MSU and one for CPP. These classifiers consisted of a principal component analysis model followed by a support vector machine (SVM). The results of the model were tested on 48 new consecutive samples retrieved from VieCuri Medical Centre. Results for MSU were compared with the 2015 ACR/EULAR Gout Classification criteria [1]. Results for CPP were compared to the newly developed CPPD classification criteria set [2]. Results: Table 2 shows the performance of the classifiers against the clinical references, which were the criteria sets. From the 48 samples, 20 were diagnosed with a crystal arthropathy according to the criteria; of which the combined approach of Raman spectroscopy and the classifier correctly identified 17. No false positives were detected, and the method had an accuracy of 93.75. Conclusions: These results demonstrate that Raman spectra can be classified with basic machine learning algorithms. This method could provide clinicians with an objective measure for easy interpretation of otherwise complex data, although verification on a larger

dataset is required. When finished, this algorithm can aid in the implementation of Raman spectroscopy into routine rheumatology practice.

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Table 2. Results of the SVM classification model predicting CPP and MSU. Measures calculated with respect for the newly developed criteria set for CPPD (positive above 57 points or with identified CPP crystals in SF) and the 2015 ACR/EULAR criteria set for gout (positive above 8 points or with identified MSU crystals in SF). Ninety-five percent confidence intervals are given for each performance measure.

	MSU Identified with Automated Classifier	CPP Identified with Automated Classifier	Negative with Automated Classifier
Gout according to criteria set	11	0	2
CPPD according to criteria set	0	6	1
Negative in both sets	0	0	28
	Gout	CPPD	Combined
Sensitivity	84.6% (CI 54.4–98.8)	85.71% (CI 42.1–99.6)	85.00% (CI 62.1–96.8)
Specificity	100% (CI 90.0–100)	100% (CI 91.4–100)	100% (CI 92.0–100)
Accuracy	95.83 (CI 85.8–99.5)	97.92% (CI 88.9–100)	93.75% (CI 82.8–98.7)
PPV	100% (CI 71.5–100)	100% (CI 54.1–100)	100% (CI 80.5–100)
NPV	94.59% (CI 81.8–99.3)	97.62% (CI 87.4–99.9)	90.32% (CI 74.3–98.0)
Kappa	0.89 (near perfect)	0.91 (near perfect)	0.86 (near perfect)

4. In-Hospital Treatment, Secondary Prevention and Mortality after First-Ever Acute Myocardial Infarction in Patients with Gout

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Abstract: Background: Patients with gout are at increased risk of acute myocardial infarction (AMI) [1]. The clinical course, secondary prophylaxis and mortality after AMI has not been previously studied. The aim of this study was to investigate the in-hospital treatment, secondary prevention and all-cause and cardiovascular disease (CVD)-related mortality after the first-ever AMI in patients with gout compared to the general population. Methods: Using data from population-based registers, we identified all patients in Western Sweden with a diagnosis of gout at both primary and specialty care and a first-ever AMI in the period 2006–2016. Up to five individually matched controls with a first-ever AMI (matched on sex and admission year) were identified as comparators. Follow-up started at the date of admission for the first-ever AMI and ended at death, emigration or 365 days of follow-up after the AMI, whichever occurred first. The in-hospital treatment and secondary prevention in gout cases and controls were compared by using logistic regression analysis with adjustments for age. Cox regression analysis was used to assess the 1-year mortality with adjustments for age, baseline comorbidities, and medication within 6 months before the start of follow-up. Results: We identified 1000 patients with gout and a first-ever AMI (men, 72.7%; mean age, 70.0 years) and 4740 matched general population comparators (men, 73.5%; mean age, 71.5 years). At admission, patients with gout had significantly more comorbidities (Table 3). The in-hospital treatment differed significantly between cases and controls. Patients with gout were more likely to receive treatment with diuretics and

continuous positive airway pressure and less likely to undergo coronary angiography, percutaneous coronary intervention (PCI) or any primary reperfusion (Table 4). At discharge, patients with gout were less often prescribed statins and more often prescribed nitrates, diuretics, digitalis and calcium antagonists (Table 4). The 1-year all-cause and CVD-related mortality was significantly higher in gout patients as compared to the general population (HR, 1.84; 95% CI, 1.52–2.23; and HR, 1.75; 95% CI, 1.38–2.21, respectively) (Figure 1). Conclusions: Patients with gout were less likely to undergo coronary angiography and PCI during hospitalization for the first-ever AMI and were less likely to be prescribed statins at discharge compared to the general population. The all-cause and CVD-related mortality was significantly higher in patients with gout, which might be partly related to differences in in-hospital treatment and secondary prevention.

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Table 3. Patient characteristics and comorbidities in gout patients and general population comparators at admission for the first-ever AMI.

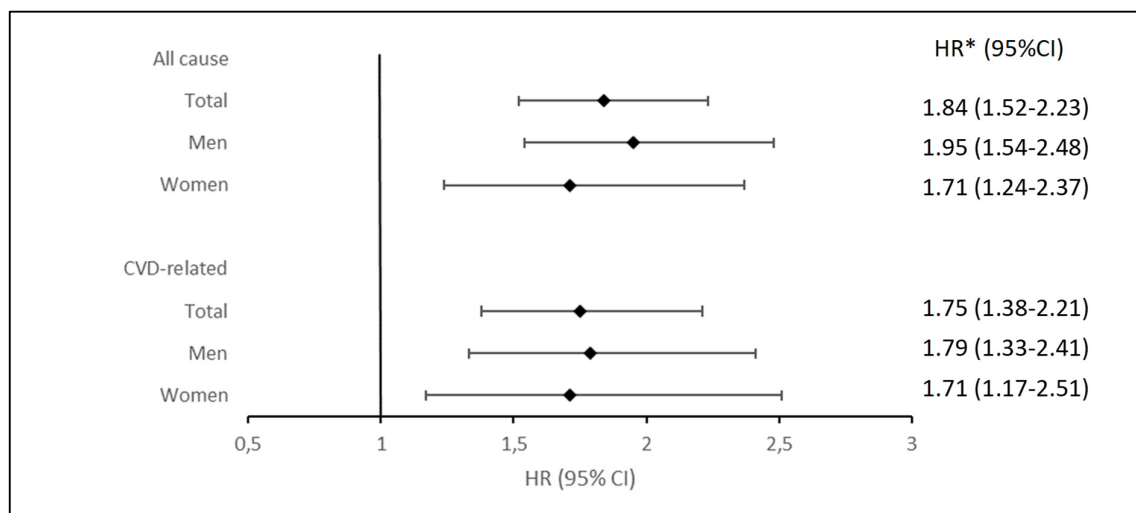
	Gout Cases N = 1000	Controls § N = 4740	p-Value	OR * (95%CI)
Men, N (%)	727 (72.7)	3485 (73.5)	0.5925	
Age, mean (SD), years	70.0 (11.6)	71.5 (11.3)	0.0001	
Comorbidities, N (%)				
CHD	284 (28.4)	978 (20.6)	<0.0001	1.5 (1.3–1.7)
Hypertension	823 (82.3)	2661 (56.1)	<0.0001	3.6 (3.1–4.3)
Diabetes	309 (30.9)	857 (18.1)	<0.0001	2.0 (1.7–2.3)
Obesity	271 (27.1)	793 (16.7)	<0.0001	2.0 (1.7–2.3)
Hyperlipidemia	404 (40.4)	1271 (26.8)	<0.0001	1.9 (1.6–2.1)
Renal disease	225 (22.5)	405 (8.5)	<0.0001	3.1 (2.6–3.7)
Heart failure	207 (20.7)	406 (8.6)	<0.0001	2.7 (2.2–3.3)
Cardiomyopathy	12 (1.2)	24 (0.5)	0.01	2.4 (1.2–4.9)
Atrial fibrillation	212 (21.2)	466 (9.8)	<0.0001	2.4 (2.0–2.9)
Smoking	185 (18.5)	1017 (21.5)	0.03	0.9 (0.7–1.1)
Alcoholism	47 (4.7)	93 (2.0)	<0.0001	2.7 (1.9–3.9)
Cerebrovascular disease	205 (20.5)	598 (12.6)	<0.0001	1.7 (1.4–2.0)
Thromboembolic disease	19 (1.9)	70 (1.5)	0.33	1.2 (0.7–2.1)
Malignancy	95 (9.5)	366 (7.7)	0.06	1.2 (1.0–1.6)
Atherosclerotic disease	113 (11.3)	252 (5.3)	<0.0001	2.2 (1.7–2.7)
Medication, N (%)				
CVD drugs □	733 (73.3)	2323 (49.0)	<0.0001	2.9 (2.5–3.3)
Anticoagulants	462 (46.2)	1408 (29.7)	<0.0001	2.0 (1.7–2.3)
Allopurinol	350 (35.0)	32 (0.7)	<0.0001	78.5 (54.2–113.8)
Colchicine	3 (0.3)	5 (0.1)	0.13	3.2 (0.8–13.3)
Cortisone	149 (14.9)	259 (5.5)	<0.0001	2.9 (2.4–3.7)

§ Matched on sex and admission year. *Adjusted for age. □ Vasodilator drugs, anti-hypertensive drugs, diuretics, beta-blockers, calcium antagonists and renin-angiotensin-aldosterone inhibitors. AMI, acute myocardial infarction; CHD, coronary heart disease; CVD, cardiovascular; OR, odds ratio; CI, confidence interval.

Table 4. In-hospital treatment and medication prescribed at discharge after the first-ever AMI in gout patients and general population comparators.

	Gout Cases N = 1000	Controls § N = 4740	p-Value	OR * (95%CI)
In-hospital treatment, N (%)				
Beta blockers iv	107 (10.7)	449 (9.5)	0.23	1.2 (0.9–1.4)
Diuretics iv	232 (23.2)	824 (17.4)	<0.0001	1.4 (1.2–1.6)
Anticoagulants iv	657 (65.7)	3116 (65.7)	0.98	1.0 (0.9–1.1)
Inotropes iv	43 (4.3)	159 (3.4)	0.14	1.3 (0.9–1.8)
Nitrates iv	91 (9.1)	394 (8.3)	0.42	1.1 (0.9–1.4)
Coronary angiography	726 (72.6)	3734 (78.8)	<0.0001	0.8 (0.7–0.9)
Any primary reperfusion	238 (23.8)	1459 (30.8)	<0.0001	0.7 (0.6–0.7)
PCI	231 (23.1)	1408 (29.7)	<0.0001	0.7 (0.6–0.9)
Acute CABG	3 (0.3)	13 (0.3)	0.89	1.2 (0.3–4.0)
CPAP	69 (6.9)	190 (4.0)	0.0001	1.7 (1.3–2.3)
PM/ICD	19 (1.9)	53 (1.1)	0.04	1.7 (1.0–2.8)
Medication at discharge, N (%)				
RAAS inhibitors	709 (70.9)	3311 (69.9)	0.51	1.1 (0.9–1.3)
Beta blockers	838 (83.8)	4064 (85.7)	0.11	0.9 (0.7–1.1)
Antiplatelets	938 (93.8)	4509 (95.1)	0.08	0.8 (0.6–1.1)
Calcium antagonists	217 (21.7)	643 (13.6)	<0.0001	1.7 (1.5–2.1)
Digitalis	40 (4.0)	81 (1.7)	<0.0001	2.2 (1.5–3.3)
Diuretics	399 (39.9)	1079 (22.8)	<0.0001	2.2 (1.9–2.6)
Nitrates	185 (18.5)	609 (12.8)	<0.0001	1.5 (1.2–1.8)
Statins	771 (77.1)	3963 (83.6)	<0.0001	0.7 (0.6–0.9)

§ Matched on sex and admission year. * Adjusted for age. AMI, acute myocardial infarction; iv, intravenous; PCI, percutaneous coronary intervention; CABG, coronary artery by-pass grafting; CPAP, continuous positive airway pressure; PM, pacemaker; ICD, implantable cardioverter defibrillator; RAAS, renin-angiotensin-aldosterone system; OR, odds ratio; CI, confidence interval.

**Figure 1.** All cause and CVD-related mortality at 1 year after the first-ever AMI in patients with gout compared to the general population. *Adjusted for age, baseline comorbidities and medication within 6 months before the start of follow-up. HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease.

5. Using a New Engineering Method, Single-Shot Computational Polarized Light Microscopy (SCPLM), in Identifying Crystals in Synovial Fluid

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Abstract: Background: The gold standard for crystal arthritis diagnosis relies on identification of either monosodium urate (MSU) or calcium pyrophosphate (CPP) crystals in synovial fluid by compensated polarized light microscope (CPLM). However, CPLM analysis is labor intensive and depends on technician expertise. We previously described single-shot computational polarized light microscopy (SCPLM), which detects MSU and CPP crystals in synovial fluid [1]. This work evaluates the reliability and validity of crystal detection for SCPLM images using crystal experts. Methods: Microscope slides from patients with CPP or MSU crystals in synovial fluid were obtained and de-identified. Digital images were acquired using an Olympus IX83 microscope, standard objective lens (100×/1.4NA) and either CPLM or SCPLM methodology. Briefly, SCPLM uses a CMOS sensor where each pixel is integrated with a directional polarizing filter with four axes of polarization (0°, 90°, 45°, 135°). SCPLM further combines images from multiple focal depths into a single bright-field fused image. In random order, raters were presented paired CPLM images and a single bright-field fused SCPLM image for 67 FOV (including 7 negative controls). For each FOV and each method, each rater recorded their level of certainty (1–5) and crystal type for each suspect crystal. Crystals rated 3 or higher by both raters (++) on either method were included in a high-certainty crystal subset. After rating all of the FOV, raters were presented with side-by-side FOV (CPLM vs. SCPLM) and asked for their preferred image. Results: Sixty-seven FOV were imaged by CPLM and SCPLM methodologies (29 CPP, 31 MSU and 7 negative controls). With a specified limit of 15 crystals per FOV, 377 unique crystals were identified: 280 CPP, 87 MSU and 10 uncertain or discrepant crystal identity. All suspect crystals that were rated low certainty came from negative control FOVs. Raters identified a higher number of crystals by SCPLM over CPLM for both CPP and MSU (Table 5). SCPLM identified 239/280 CPP crystals and 86/87 MSU crystals whereas CPLM identified 138/280 CPP and 48/87 MSU. For SCPLM, there were only 11/239 CPP crystals (4.6%) where neither rater was certain; for CPLM, there were 13/138 (9.4%) where neither rater was certain. The area under the curve (AUC) was higher for SCPLM compared to CPLM for both raters (0.765 and 0.80 vs 0.61 and 0.61, respectively). To compare methods, we focused on the 144 CPP and 69 MSU crystals where both raters were certain (++) about the crystal. For 80–90% of included crystals, SCPLM was ++. In contrast, only 40–51% of crystals were CPLM ++ (Table 6). When CPLM was negative, SCPLM was certain in almost all cases. Finally, raters subjectively preferred SCPLM over CPLM in side-by-side comparison (Figure 2). They were indifferent between methodology for the negative FOVs. Conclusions: Subjective and objective measures of greater detection and higher certainty were observed for SCPLM images over standard CPLM images, particularly notable for CPP crystals. The digital data associated with these images can be incorporated into an automated scanning platform that provides a quantitative report on crystal count and morphology, which can deepen insight and impact clinical care.

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Table 5. Agreement between raters for all MSU or CPP crystals identified by either rater by either method.

CPP (n = 280 crystals)									
SCPLM					CPLM				
R1 R2	Certain	Possible	Negative		R1 R2	Certain	Possible	Negative	
Certain	89	30	90	209	Certain	44	1	69	114
Possible	3	3	6	12	Possible	1	0	7	8
Negative	16	2	18	239	Negative	10	6	16	138
	108	35	96			55	7	76	
MSU (n = 87 crystals)									
SCPLM					CPLM				
R1 R2	Certain	Possible	Negative		R1 R2	Certain	Possible	Negative	
Certain	58	5	13	76	Certain	33	1	12	46
Possible	0	0	3	3	Possible	0	0	0	0
Negative	6	1	7	7	Negative	2	0	2	2
	64	6	16	86		35	1	12	48

Table 6. Certainty of crystal by rater and method.

SCPLM	CPLM	CPP (n = 144)	MSU (n = 69)
++	++	20%	42%
++	Other	60%	48%
Other	++	20%	9%

++ = both raters with high certainty about crystal for a specific method.

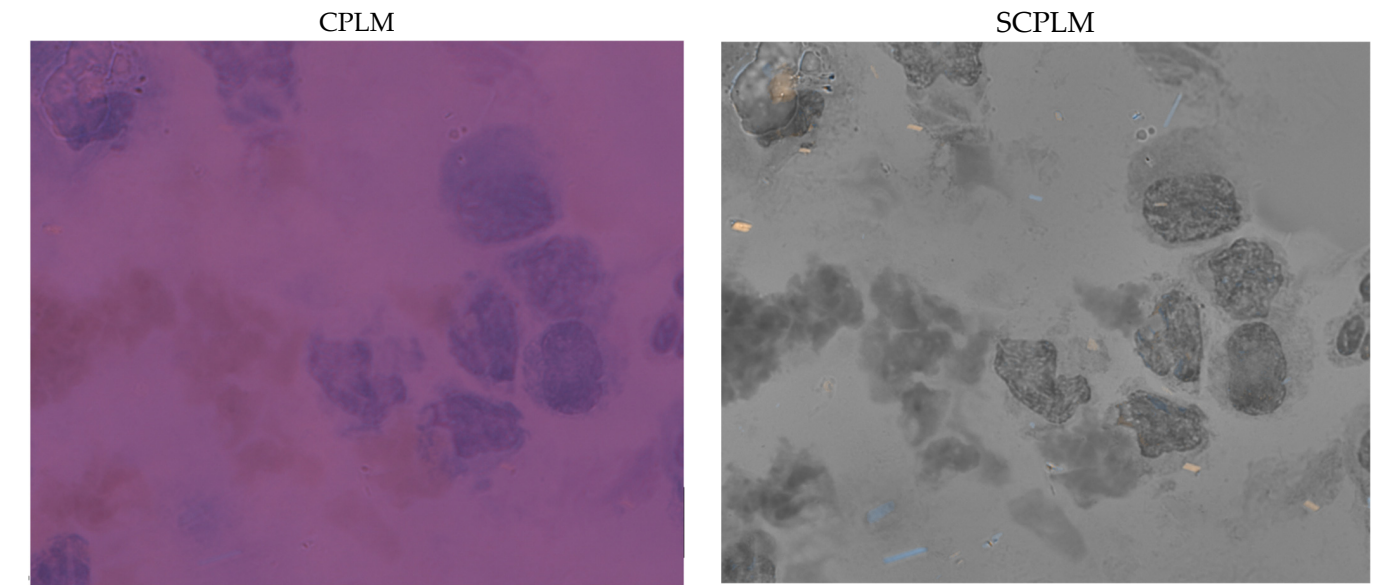


Figure 2. CPLM (compensated polarized light microscopy) and SCPLM (single-shot compensated polarized light microscopy) side-by-side field of view (100×).

6. Skeletal Muscle Mass and Quality in Gout Patients Versus Non-Gout Controls: A Computed Tomography Imaging Study
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Abstract: Background: Sarcopenia is characterized by low muscle strength or function plus low muscle quantity or quality and correlates with physical disability, poor quality of life and death [1]. While common among older adults, sarcopenia is not exclusively a phenomenon of aging, as sarcopenia prevalence is increased in a number of autoimmune and autoinflammatory conditions [2]. We assessed whether patients with gout exhibit significantly lower lumbar muscle quantity and quality versus controls, which could indicate an association between gout and sarcopenia. Methods: Fifty gout subjects and 25 controls, ages 45–80, were enrolled in a previously reported study examining spinal monosodium urate deposition. All gout subjects met 2015 ACR gout classification criteria, with entry serum urate (SU) of >6.8 mg/dL (>6.0 mg/dL if on urate-lowering therapy for <6 months). Data on demographics, gout history, exercise frequency and medical comorbidities were collected, and subjects underwent dual-energy computed tomography imaging of the lumbosacral spine. Muscle quantity (skeletal muscle area and index) and quality (skeletal muscle radiation attenuation (SMRA) and intermuscular adipose tissue (IMAT) area and index) of the psoas muscle, a previously validated muscle for assessing sarcopenia, and erector spinae muscles were measured at the L3 level (Figure 3). Results: Sixty-four subjects (41 gout and 23 controls) were included in the current analysis. Gout subjects had higher BMI, greater incidence of kidney disease and hypertension, lower exercise frequency and higher mean serum urate and creatinine vs. controls. Lumbar SMRA was significantly lower in gout subjects vs. controls (gout, median 32.5 HU, IQR 20.9–39.6; controls, median 39.2 HU, IQR 31.8–43.2, $p = 0.009$) (Figure 4). Lumbar IMAT area was significantly higher in gout subjects vs. controls (gout, median 6.84 cm², IQR 4.78–10.17; controls, median 4.88 cm², IQR 3.49–6.44, $p = 0.007$), as was lumbar IMAT index (gout, median 2.23 cm²/m², IQR 1.60–3.39; controls, median 1.56 cm²/m², IQR 1.17–2.17, $p = 0.008$) (Figure 4). These differences persisted after adjusting for potential confounders. There was no significant difference between gout and control groups in lumbar skeletal muscle area (gout, median 73.9 cm², IQR 64.3–85.9; controls, median 73.8 cm², IQR 69.3–82.5, $p = 0.74$) or lumbar skeletal muscle index (gout, median 24.4 cm²/m², IQR 21.0–27.6; controls, median 24.4 cm²/m², IQR 22.5–28.4, $p = 0.44$), indicating no difference in total muscle quantity (Figure 4). Conclusions: Patients with gout have decreased muscle quality compared with controls, suggesting an association between gout and sarcopenia. Elucidating the relationship between sarcopenia and gout may provide opportunities to better manage the impact of gout on patients' physical function.

1. Bennett, J.L.; Pratt, A.G.; Dodds, R.; Sayer, A.A.; Isaacs, J.D. Rheumatoid sarcopenia: loss of skeletal muscle strength and mass in rheumatoid arthritis. *Nat. Rev. Rheumatol.* **2023**, *19*, 239–251.
2. An, H.J.; Tizaoui, K.; Terrazzino, S.; Cargnin, S.; Lee, K.H.; Nam, S.W.; Kim, J.S.; Yang, J.W.; Lee, J.Y.; Smith, L.; et al. Sarcopenia in Autoimmune and Rheumatic Diseases: A Comprehensive Review. *Int. J. Mol. Sci.* **2020**, *21*, 5678.

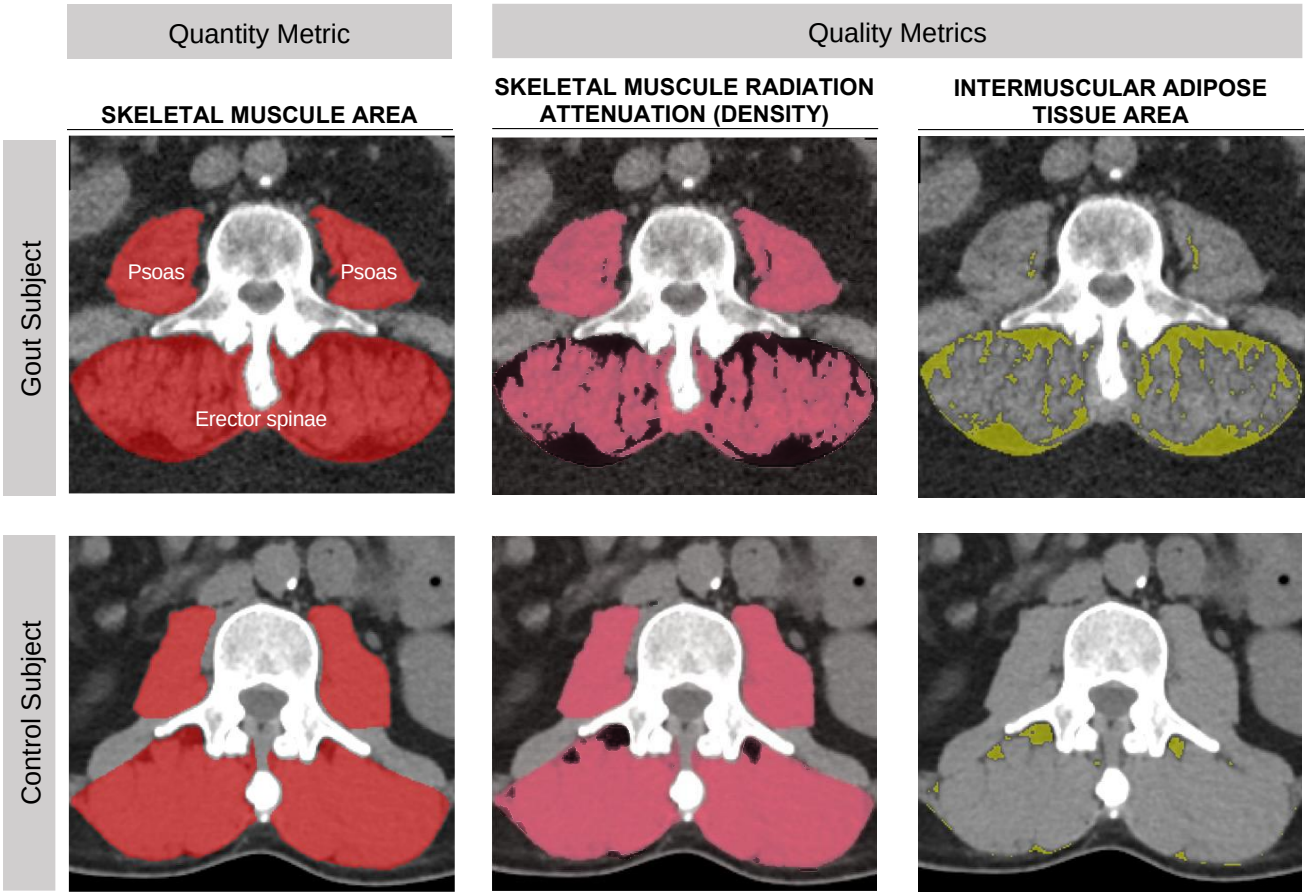


Figure 3. Representative CT images of lumbar muscle quantity and quality metrics in a gout subject vs. a control subject.

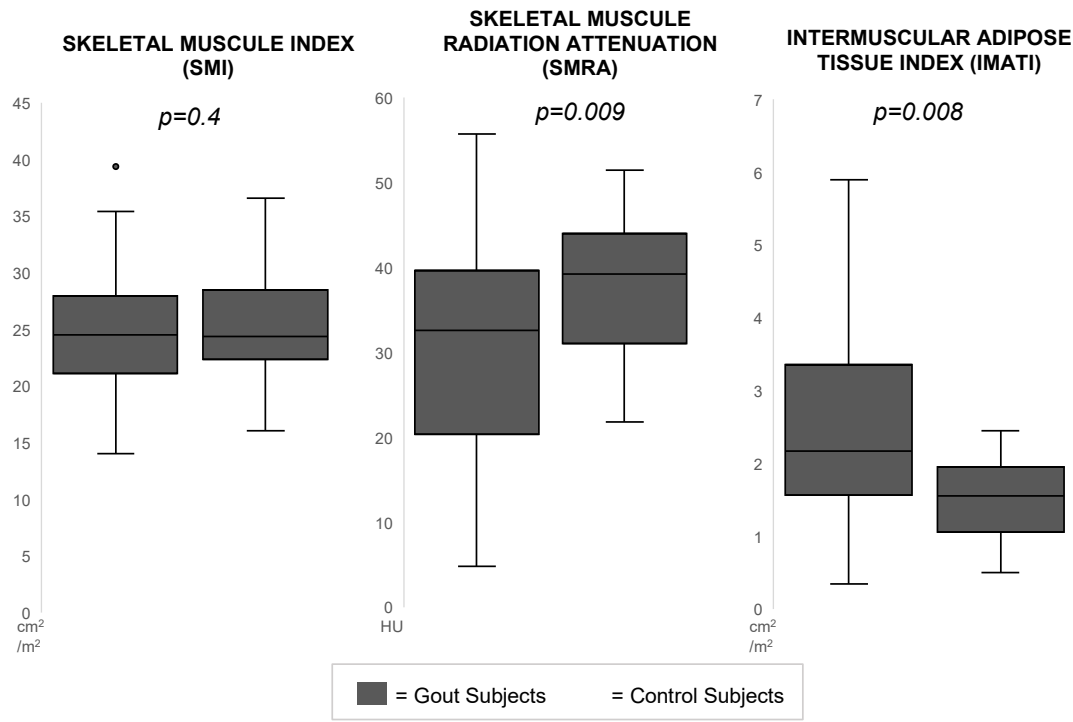


Figure 4. Lumbar skeletal muscle index, skeletal muscle radiation attenuation (density) and inter-muscular adipose tissue index in gout vs. control subjects.

7. An Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials on the Initiation of Urate-Lowering Therapy during a Gout Flare

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Abstract: Background: There remains debate about the optimal time for initiating urate-lowering therapy (ULT) in the setting of a gout flare. The aim was to perform a systematic review and meta-analysis of randomized controlled trials (RCTs) assessing the initiation of ULT during a gout flare. Methods: The systematic review was conducted in accordance with PRISMA methodology. MEDLINE, EMBASE and The Cochrane Library were searched for RCTs examining the initiation of ULT during a gout flare. The quality of included studies was assessed using the Cochrane Risk of Bias 2 tool. Data were extracted for the following outcomes: patient-rated pain score, duration of gout flare, recurrent gout flares, time to achieve target serum urate, adherence to ULT, patient satisfaction with treatment and adverse events. Meta-analyses were performed using Review Manager v5.4. Results: A total of 972 studies were identified and, of these, 6 RCTs met the criteria for inclusion in the analysis. Three studies were assessed as having high risk of bias, two studies as having low risk of bias and one study with some concerns. There was a total of 445 pooled participants; 226 participants randomized to early initiation of ULT and 219 to placebo or delayed initiation of ULT. Few participants (*n* = 62, 13.9%) had tophaceous gout. Allopurinol was used in three studies, febuxostat in two studies and probenecid in one study. There were no statistical differences in patient-rated pain scores on days 3–4 (SMD −0.01; 95% CI −0.21–0.18; *p* = 0.88), days 7–8 (SMD 0.07; 95% CI −0.13–0.27; *p* = 0.50) or days 14–15 (SMD −0.08; 95% CI −0.36–0.20; *p* = 0.57). Additionally, there was no difference in time to resolution of gout flare (SMD 0.77 days; 95% CI −0.26–1.79; *p* = 0.14; Figure 5) or the risk of recurrent gout flare within the subsequent 28 to 30 days (RR 1.06; 95% CI 0.59–1.92; *p* = 0.84; Figure 6). Adverse events were similar between groups. The included studies did not examine time to achieve target serum urate, long-term adherence to ULT or patient satisfaction with treatment. Conclusions: There appears to be no indication for harm or for benefit to initiating ULT during a gout flare. These findings, however, may not be applicable to patients with more advanced gout or tophaceous gout. We recommend an individualized approach to patient management.

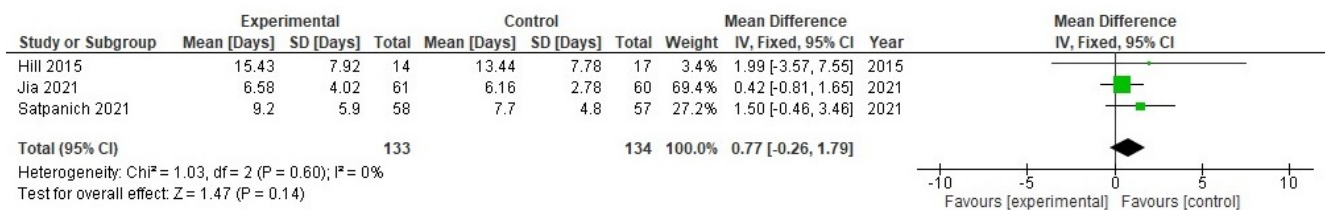


Figure 5. Forest plot of the days to gout flare resolution between the experimental group (early initiation of ULT) and control group (placebo or delayed initiation of ULT).

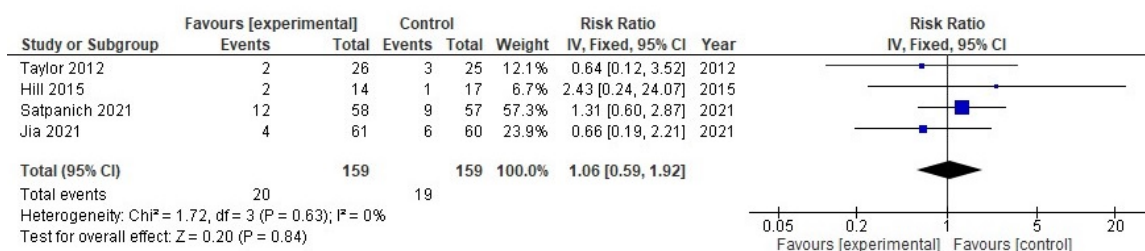


Figure 6. Forest plot of the risk of recurrent gout flare within the subsequent 28 to 30 days between the experimental group (early initiation of ULT) and the control group (placebo or delayed initiation of ULT).

8. Sex-Specific Differences in Cytokine Levels in Patients with Gout Compared to Controls

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Abstract: Background: Gout is an inflammatory disease orchestrated by innate immune mechanisms around interleukin-1 β activation and release. Gout is more prevalent in men compared to women, and clinical profiles of patients with gout are reported to differ by sex. This study aimed to investigate sex-specific cytokine profiles in circulation and in stimulated peripheral blood mononuclear cells (PBMCs) of patients with gout and controls. Methods: Participants in the gout group were included based on at least one clinically diagnosed gout flare and either proven presence of MSU crystals in the synovial fluid or a score of at least 8 according to American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) ($n = 146$). The control group included individuals with varying levels of serum urate and absence of gout ($n = 261$). PBMCs were treated in vitro for 24h with various stimuli in order to assess innate immune responses (e.g., lipopolysaccharide, C16 with or without monosodium urate crystals, heat killed *C. albicans*, *S. aureus*, *Mtb*). Cytokines were determined in culture supernatants and plasma by ELISA. For the cytokine production analysis, a linear model was created using the ‘lm’ function in R. The model was run three times: for all data with sex and age as covariates and separately for women and men, disregarding the correction factor for “sex.” Results: Plasma IL-1Ra and hsCRP were higher in men with gout compared to men without gout whereas no significant differences in circulating cytokines were observed in women. Overall, PBMCs of gout patients show higher production of IL-1 β , IL-1Ra and TNF upon 24h stimulation with TLR ligands or bacterial stimuli. This elevated cytokine production in response to stimulation of PBMCs was observed predominantly in women while these differences were less consistent in men. Conclusions: Patients with gout show an increased in vitro cytokine production compared to individuals without gout. We identified sex-specific cytokine production in gout in response to in-vitro stimulation. While men with gout had higher levels of circulating cytokines, PBMCs of women with gout showed an increased cytokine production capacity. Recent studies show that clinical profiles of patients with gout are reported to differ by sex, older age, higher prevalence of comorbidities and use of diuretics have been reported more

in women and high consumption of alcohol, especially beer, in men. These data suggest potentially different regulatory mechanisms of inflammation in men and women with gout.

9. Socioeconomic Disadvantage and Outpatient Follow-Up after an Emergency Department Visit for Acute Gout Flare

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Abstract: Background: Although persons from underserved groups more frequently utilize the emergency department (ED) for gout flares and are more likely to be hospitalized due to gout, there is a gap in our understanding of whether these patients are retained in care after their visit to the ED. Our objective was to determine whether socioeconomic disadvantage, assessed using the area deprivation index (ADI), is associated with the rate of outpatient follow-up among people with gout treated in EDs. Methods: This cohort included patients with a confirmed gout flare at three EDs that were identified using an electronic medical record (EMR) gout alert system and manual EMR review. Medical record reviews were conducted to determine the presence or absence of an outpatient follow-up visit addressing gout. Adjudicated consensus and kappa coefficients were found to estimate interrater reliability. Each patient's nine-digit zip code was determined from addresses on file in order to calculate their ADI score with higher ADIs representing more socioeconomic deprivation. Univariable and multivariable logistic regression was used to test the association between ADI and outpatient follow-up for gout. Results: From 1 September 2021, to 31 August 2022, there were 1290 unique encounters among 981 patients identified by the gout flare alert as possibly having an acute gout flare. Of these, 63 patients were excluded due to participation in an ongoing randomized clinical trial testing a behavioral intervention to improve gout care. Of the remaining 918 patients, 159 patients (17%) (Table 7) had a true gout flare by manual EMR review by two assessors, who independently reviewed data. The kappa coefficient for agreement between the consensus determination of acute flare was 0.85. Of those with an acute gout flare, 120 (75.5%) were men and 113 (75.3%) were Black or African American. A total of 159 (53%) patients with an acute gout flare followed up with an outpatient provider in our healthcare system, and only 56 patients (35.2%) had an outpatient visit addressing gout (Table 8). In our cohort, the median state ADI score was 6.5 and the median national ADI score was 84. Overall, 41 patients (28.9%) resided in the least deprived state quartile (quartile 1) and 30 (21.1%) lived in the most deprived state quartile. State ADI and national ADI scores were not significantly associated with gout follow-up care in univariable analysis; however, higher ADI quartile correlated with unmarried status ($p = 0.01$). In a multivariable logistic regression model, people who reported being married were more likely to achieve outpatient follow-up gout care (OR = 2.75, 95% CI 1.28–5.93, $p = 0.01$). State ADI and national ADI scores were not significantly associated with gout follow-up care in this model. For every 10 years of increased age, the odds of achieving gout follow-up care increased by 43.6% ($p = 0.01$). Conclusions: We found that living in areas with higher socioeconomic deprivation is not associated with receipt of outpatient

follow-up visits after an acute gout flare. Age and marital status are factors associated with a patient's probability of obtaining outpatient follow-up for gout.

Table 7. Demographic characteristics of participants who presented to the emergency department with an acute gout flare and further characterized by presence or absence of outpatient gout follow-up care.

Characteristics	Total, N = 159	Gout Follow-Up Care, N = 56	No Gout Follow-Up Care, N = 103	p-Value
Age, years, mean (SD)	54.2 (14.0)	58.0 (15.4)	52.2 (12.8)	0.02
Sex, male, N (%)	120 (75.5)	41 (73.2)	79 (76.7)	0.6
Race/Ethnicity, N (%) *				
Black or African American	113 (72.4)	43 (79.6)	70 (68.6)	0.4
White	37 (23.7)	10 (18.5)	27 (26.5)	
Other **	6 (3.8)	1 (1.9)	5 (4.9)	
Area deprivation index (ADI) ranking, state decile, median (Q 25–Q 75) #	6.5 (3–9)	7 (3–9)	6 (3–9)	0.7
Quartile 1 (least disadvantaged), N(%)	41 (28.9)	14 (27.5)	27 (29.7)	0.9
Quartile 2, N(%)	30 (21.1)	10 (19.6)	20 (22.0)	
Quartile 3, N(%)	41 (28.9)	17 (33.3)	24 (26.4)	
Quartile 4 (most disadvantaged), N(%)	30 (21.1)	10 (19.6)	20 (22.0)	
Area deprivation index (ADI) ranking, national percentile, median (Q 25–Q 75) ##	84 (58.8–96)	86 (59–96)	83 (56–96)	0.8
Quartile 1 (least disadvantaged), N(%)	35 (24.6)	12 (23.5)	23 (25.3)	0.8
Quartile 2, N(%)	37 (26.1)	12 (23.5)	25 (27.5)	
Quartile 3, N(%)	40 (28.2)	17 (33.3)	23 (25.3)	
Quartile 4 (most disadvantaged), N(%)	30 (21.1)	10 (19.6)	20 (22.0)	
Marital Status, N (%) ***				0.003
Married	64 (41.6)	31 (57.4)	33 (33.0)	
Not Married	90 (58.4)	23 (42.6)	67 (67.0)	
Medication prescribed at ED discharge, N (%) †				
Corticosteroids	91 (57.2)	31 (55.4)	60 (58.3)	0.7
Opioids	89 (56.0)	32 (57.1)	57 (55.3)	0.8
NSAIDs	66 (41.5)	27 (48.2)	39 (37.9)	0.2
Colchicine	53 (33.3)	23 (41.1)	30 (29.1)	0.1
Allopurinol	16 (10.1)	7 (12.5)	9 (8.7)	0.6
Anakinra	5 (3.1)	3 (5.4)	2 (1.9)	0.3
Local injection	10 (6.3)	6 (10.7)	4 (3.9)	0.2

* Missing for 3 individuals. ** Includes Hispanic/Latino, American Indian or Alaska Native, Asian, Native Hawaiian/Other Pacific Islander. *** Not Married includes single, divorced, separated, widowed; missing for 5 individuals. # State decile from 1 (least disadvantaged) to 10 (most disadvantaged). ## National percentile from 1 (least disadvantaged) to 100 (most disadvantaged). † Categories are not mutually exclusive. ED, emergency department; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 8. Healthcare utilization among participants following an emergency department encounter for acute gout flare including emergency department visits, hospitalizations, follow-up with type of provider and interval to follow-up and proportion of patients with outpatient visits that addressed gout.

Healthcare Outcome	Gout Follow-Up care, N = 56	No Gout Follow-Up Care, N = 103	p-Value
Hospitalized, N (%)	7 (12.5)	9 (8.7)	0.5
Received Care at Emergency Department or Urgent Care, N (%)	19 (33.9)	32 (31.1)	0.7
Outpatient Service Addressing Gout, N (%)			
Internal Medicine Subspecialties (including Rheumatology) ^α	20 (35.7)		
General Internal Medicine	14 (25.0)		
Surgical Subspecialty ^β	9 (16.1)		
Family Medicine	8 (14.3)		

Table 8. Cont.

Healthcare Outcome	Gout Follow-Up care, N = 56	No Gout Follow-Up Care, N = 103	p-Value
Palliative Care and Geriatrics	3 (5.4)		
Podiatry	1 (1.8)		
Weight Loss Management	1 (1.8)		
Timing of Gout Outpatient Follow-up Visit since ED Visit, N (%)			
≤1 month since index ED visit	40 (71.4)		
>1 month and ≤3 months since index ED visit	7 (12.5)		
>3 months since index ED visit	9 (16.1)		

α Internal medicine subspecialties included cardiology, endocrinology, nephrology, oncology, infectious disease, pain management, urology, hepatology, psychiatry, occupational medicine. β Surgical subspecialties included neurosurgery, plastic surgery, thoracic surgery, vascular surgery, orthopedics, kidney transplant, bone marrow transplant. ED, emergency department.

10. Clustering of Gout-Related Comorbidities and Their Relationship with Gout Flares: A Data-Driven Cluster Analysis of Eight Comorbidities

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Abstract: Objective: To study the aggregation of multiple comorbidities in people with gout and explore differences in the prognosis of gout flares among different subgroups. Methods: The retrospective study included gout patients from the Department of Endocrinology and Metabolism of the Tenth People’s Hospital Affiliated to Tongji University as the research subjects. Eight comorbidity variables such as obesity, type 2 diabetes, hypertension, cardiovascular disease, chronic kidney disease, dyslipidemia, increased liver enzyme levels and cancer were used as research indicators. Cluster analysis was performed to measure the proximity of gout-related comorbidities, and hierarchical clustering was conducted to determine the subgroups of homogeneous gout patients. Patients with gout were followed for 1 year for acute gout flares to explore differences in prognosis between subgroups. Results: Cluster analysis divided the eight comorbidity variables into three categories: first, type 2 diabetes, hypertension, cardiovascular disease, chronic kidney disease and cancer; second, dyslipidemia; third, obesity and increased liver enzyme levels. In the cross-sectional study, we recruited a total of 2639 people with gout, with an average age of 50.6 years and 95% male. Five groups (C1-C5) of patients with gout were identified with significantly different patient characteristics and clusters of comorbidities. C1 ($n = 671$, 25%) was characterized by isolated gout with few comorbidities; C2 ($n = 258$, 10%) were all obese, with the youngest age (mean 40 years). C3 ($n = 335$, 13%) was almost all diabetic patients (99.7%), and the course of gout was the longest (average 8 years). C4 ($n = 938$, 36%) had the largest number of patients, and all patients had dyslipidemia. C5 ($n = 437$, 16%) included the highest proportion of people with cardiovascular disease (53%), chronic kidney disease (56%) and cancer (7%), with the oldest age (mean 65 years). In the follow-up study, a total of 463 patients completed a 1-year follow-up on gout flares (Figures 7 and 8). Among them, C2 (gout and obesity) had the lowest rate of gout flares (52.1%) and the latest occurrence of gout flares (average 10 months). Conversely, C5 (gout with cardiovascular disease, chronic kidney disease or cancer) had the highest rate of gout flares (71.9%) and the earliest onset of gout flares (mean 3 months). Conclusions: We clustered people with gout into five groups with varying comorbidities. Gout patients with cardiovascular disease, chronic kidney disease or cancer are at the highest risk of acute gout flares and should be given more comprehensive care by clinicians.

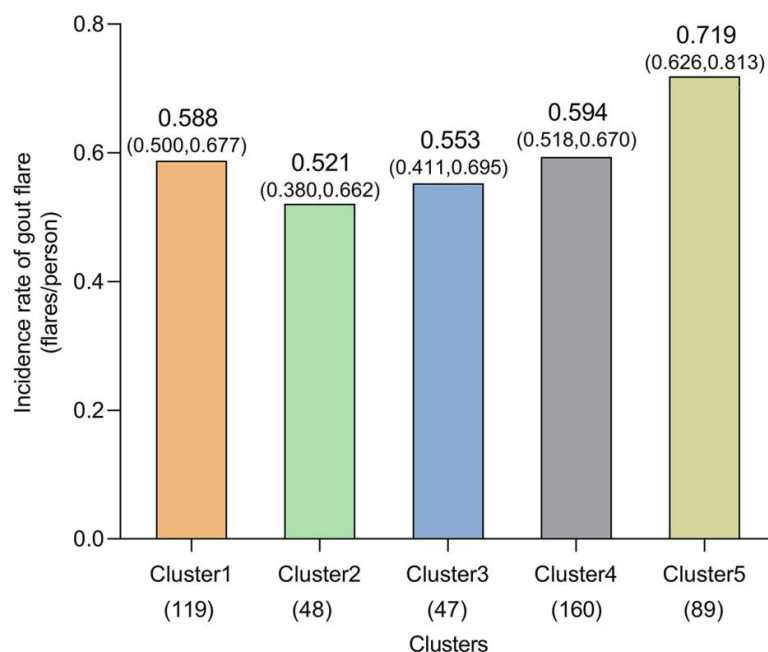
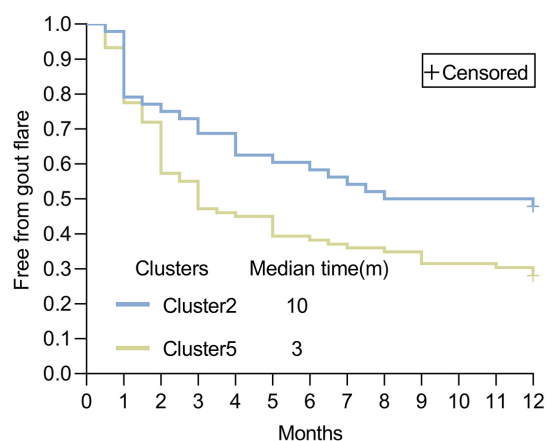


Figure 7. Incidence rate of gout flare within 1 year.



Clusters	Months												
	0	1	2	3	4	5	6	7	8	9	10	11	12
Cluster2	48	38	36	33	30	29	28	26	24	24	24	24	23
Cluster5	89	69	51	42	40	35	34	32	31	28	28	27	25

Figure 8. Kaplan–Meier curve for time to first gout flare in group C2 and C5.

11. Sex Ratios in Gout

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Abstract: Background: Gout has traditionally been thought of as a male disease. This may have resulted in an under-diagnosis of gout in women. Given that gout definitions vary substantially in the literature and that serum urate levels in women are about 1 to 1.5 mg/dL lower than those in men, it is possible that women with gout are underrepresented in research. Here, we aimed to determine the sex ratios for gout associated with different gout definitions. We then aimed to identify gout definitions that are more or less likely to include

women with gout. **Methods:** We identified studies that included both men and women with gout, restricting to those with at least 50 women published since the year 2000. We then used the number of reported incident/prevalent cases to calculate male:female sex ratios. To validate our findings, we calculated sex ratios for various gout definitions in both the UK Biobank and All of Us cohorts. **Results:** The median sex ratio for gout was 3.0, ranging from 1.2 to 17.1 (Table 9). We found that with more stringent gout definitions, fewer women were included in studies relative to men. This was especially apparent for clinical trials that only included individuals above a serum urate threshold, resulting in the highest sex ratios of all studies. In the UK Biobank and All of Us cohorts, we were able to reproduce these results, with the least stringent criteria (self-reported gout or gout code or ULT) resulting in sex ratios of 8.0 and 1.7, respectively, and the most stringent criteria (self-reported gout and gout code and ULT) resulting in sex ratios of 13.0 and 3.3, respectively (Table 10). **Conclusions:** Disease definitions are important to consider when attempting to include under-represented groups in research. With increasing stringency for definitions of gout, we found that fewer women were included relative to men. Most importantly, this resulted in few female gout cases being included in clinical trials. Caution should be taken when considering inclusion in gout research to not further bias research toward over-represented groups. A second interesting finding was the dramatic difference in sex ratio between the US-based All of Us cohort and the UK-based UK Biobank. There are several possibilities for why this may have occurred, including the restricted age range of the UK Biobank (40–70 years) compared to All of Us (>18 years) and the ethnicity differences between cohorts. However, when applying different gout criteria to White All of Us participants between 40 and 70, we found similar results to the full cohort. It could therefore be the case that female gout is relatively less common in the UK compared to the US, or perhaps it is less likely to be ascertained in a population-based research cohort.

Table 9. Sex ratios for various gout definitions in reviewed literature including both men and women with gout published since the year 2000. Publications with fewer than 50 women with gout excluded. Included the most recent publication for each cohort. Sex ratios all calculated as ratio of number of incident or prevalent gout cases, rather than using the incidence/prevalence rates.

Publication (Author Year PMID)	Definition	N	Sex Ratio (M:F)
Mikuls 2005 15647434	Oxford Medical Information Systems code for clinically diagnosed gout	56,483	3.9
Harrold 2006 16644784	Two or more ICD-9 codes for gout and on private insurance	6133	4.3
Lawrence 2008 18163497	Self-reported physician-diagnosed gout	510	2.4
Bhole 2010 20131266	Acute joint pain with swelling and heat lasting up to 2 weeks, followed by complete remission of symptoms Also needed to respond to antigout medications	304	1.9
De Vera 2010 20124358	Two ICD-9 codes at least 1 day apart	9642	1.5
Cea Soriano 2011 21371293	General practitioner diagnosed gout	24,768	2.6
	Diagnostic code of gout	18,587	1.2
Chen 2012 21761146	Diagnostic code of gout + 2 prescriptions of colchicine	2930	4.5
	Diagnostic code of gout + 2 prescriptions of colchicine and ULT	1606	5.1
	Diagnostic code of gout + 2 prescriptions of colchicine and ULT, from rheumatologist	238	6.7
Chohan 2012 22052584	ACR preliminary criteria and SU > 8 mg/dL. Excluded CKD, “secondary HU”, hypersensitivity to ULT	4101	17.1
Winnard 2012 22253023	Hospital discharge ICD gout code or allopurinol/colchicine prescription. Excluded leukemia/lymphoma for allopurinol criteria	114,318	3.0
Zhu 2012 22626509	Self-reported physician-diagnosed gout	223	2.8

Table 9. Cont.

Publication (Author Year PMID)	Definition	N	Sex Ratio (M:F)
Sicras-Mainar 2013 23313534	CIAP-2 code and ICD-9 codes, validated with patient history	3130	4.3
Trifirò 2013 22736095	ICD-9 code for gout (outpatient)	3069	2.9
Kinge 2015 25887763	ICD-10 code or ICPC-2 code for gout (primary care)	22,983	3.2
	ICD-10 code or ICPC-2 code for gout (specialist)	2797	3.8
Kuo 2015 25612613	ICD-9 code for gout and gout-specific medication	1,045,059	3.3
Richette 2015 24107981	Physician-diagnosed gout	2762	5.1
Robinson 2015 26233513	Allopurinol, colchicine or gout code, excluding blood cancer	22,768	4.4
Wändell 2015 26500085	Hospital diagnosis of gout	11,755	2.9
	At least one primary or auxiliary diagnosis of gout	22,243	2.3
Dehlin 2016 27412614	At least one primary diagnosis of gout	16,833	2.6
	At least two primary diagnoses of gout or at least one at a rheumatology visit	6184	3.8
Kapetanovic 2016 27933209	ICD-10 code for gout	17,094	2.5
Rho 2016 25277955	READ code for gout	35,339	2.6
Tung 2016 27448491	ICD-9 code for gout (outpatient or inpatient) at three or more clinic visits with ULT or combination therapy	29,765	4.7
Harrold 2017 28292303	Rheumatologist-diagnosed gout based on 1977 ARA criteria	1273	4.9
Kim 2017 28676911	Primary or secondary gout diagnosis (outpatient or hospital)	383,471	8.6
Rai 2017 28040245	At least one ICD-9/10 primary diagnosis of gout	171,165	2.1
	ICD-10 code for gout	14,113	2.1
Drivelegka 2018 29855389	At least two ICD-10 codes for gout	3755	2.9
Elfishawi 2018 29247151	ICD-9 code for gout then either ARA 1977, Rome or New York criteria for gout	271	2.6
Kapetanovic 2018 30157929	ICD-10 code for gout (primary care, inpatient, outpatient)	1272	3.9
Chen-Xu 2019 30618180	Self-reported physician-diagnosed gout	214	1.8
Huang 2019 30912848	ICD-9 code plus antigout medication	2780	1.9
Zobbe 2019 30590724	ICD-10 code for gout	45,685	2.7
Te Kampe 2021 32611671	ACR/EULAR classification criteria, most were crystal-proven	954	4.9
Dehlin 2022 35266438	ICD-10 code for gout (primary or secondary care)	728	4.7

Table 10. Sex ratios for various gout definitions in the UK Biobank and All of Us cohorts.

Cohort	Definition	N	Sex Ratio (M:F)
	Self-reported doctor-diagnosed gout (SR)	7298	12.2
	Inpatient ICD-10 code for gout (CODE)	5239	6.3
	Urate lowering therapy prescription excluding lymphoma/leukemia (ULT)	5806	11.5
	SR or CODE	10,160	8.2
UK Biobank	SR or ULT	8117	11.2
	CODE or ULT	8938	7.7
	SR or CODE or ULT	10,697	8.0
	SR and CODE	2377	13.4
	SR and ULT	4987	13.0
	CODE and ULT	2107	11.9
	SR and CODE and ULT	1825	13.0

Table 10. Cont.

Cohort	Definition	N	Sex Ratio (M:F)
All of Us	Self-reported doctor-diagnosed gout (SR)	4941	2.2
	Any SNOMED code for gout (CODE)	9012	1.9
	Urate-lowering therapy prescription excluding lymphoma/leukemia (ULT)	5913	1.9
	SR or CODE	11,971	1.9
	SR or ULT	9458	1.9
	CODE or ULT	10,871	1.7
	SR or CODE or ULT	13,609	1.7
	SR and CODE	1982	2.9
	SR and ULT	1396	3.2
	CODE and ULT	4054	2.6
	SR and CODE and ULT	1175	3.3

12. Why 6.8?

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Abstract: Background: Hyperuricemia definitions are highly variable, often defined based on the distribution of urate in the population of interest or the reported urate solubility threshold of 6.8 mg/dL. This solubility threshold was derived at a temperature of 37 °C in a 1972 publication, in which the author highlighted the extreme dependence of urate solubility on temperature. In the 2019 G-CAN consensus statement, hyperuricemia was defined as “elevated blood urate concentration over the saturation threshold.” Here, we aimed to investigate the evidence for using different hyperuricemia definitions in gout research, with a focus on the 6.8 mg/dL definition. Methods: Publications were reviewed to identify serum urate thresholds for hyperuricemia and their reported justifications. Publications of intra-articular temperatures were reviewed to identify the appropriate temperature to derive urate solubility. Finally, we reproduced the results of Loeb 1972 using the data from Allen 1965 to calculate urate solubility at internal joint temperatures. Results: Hyperuricemia was defined as serum urate levels above thresholds of 5.7 to 8 mg/dL (Table 11). Where justifications were given, the majority stated that they had arbitrarily chosen that threshold or referenced another study that arbitrarily defined hyperuricemia. In some cases, the justification was related to urate solubility, suggesting that urate was saturated above the stated threshold. Additionally, in many cases different thresholds were proposed for men vs women. Intra-articular temperatures ranged from 29.7 °C to 37 °C, in most cases measured in the knee joint, with a mean of approximately 33 °C (Table 12). At this temperature, the urate solubility threshold in the presence of physiological sodium levels (140mM) would be 5.3 mg/dL based on data from Allen 1965 and Loeb 1972 (Figure 9). Conclusions: Hyperuricemia was arbitrarily defined in almost all reviewed publications. When serum urate thresholds were based on urate solubility, they all cited the Loeb 1972 publication (or other publications citing this study), which highlighted the extreme variability of urate solubility based on temperature. Using the data presented in this paper, an estimated internal joint temperature of 33 °C would result in a urate solubility threshold of approximately 5.3 mg/dL. Importantly, this solubility threshold represents the point at which solid urate is in equilibrium with its dissolved form, and as such lower urate levels would further encourage crystal dissolution and suppress crystal growth. Sodium concentration, pH and other variables have also been shown to have large effects on urate solubility and nucleation/crystal growth. We propose that serum urate should be analyzed as a continuous variable wherever possible, in men and women separately, with results presented per unit change in serum urate. This would reflect the observation that gout risk exponentially increases with increasing urate levels. When a serum urate threshold

is required for the purpose of gout treatment, we would suggest that one should aim for serum urate levels below 6 mg/dL as an upper limit, with lower levels more likely to improve crystal dissolution.

Table 11. Hyperuricemia definitions and justifications.

Publication (Author Year PMID)	Definition SU > mg/dL	Sex	Justification/Notes
Popert 1962 14487867	6.0	Both	Upper limit of normal (arbitrarily defined)
Kellgren 1963 No PMID	6.0 7.0	Women Men	Documents the Rome 1961 conference, where the thresholds were originally proposed according to Bardin and Richette (2014)
Mikkelsen 1965 14320691	6.0	Both	They state the arbitrary definitions of hyperuricemia are unrealistically low at five for women and six for men and propose that from a population standpoint, these estimates should be based on the population distribution of urate
Hall 1967 6016478		Both	Hyperuricemia is stated as a “term of convenience rather than an accurate definition of a metabolic abnormality”
Loeb 1972 5027604	6.8		Equilibrium concentration for urate at 37 degrees in the presence of physiological levels of Na ⁺ (140mM)
Wallace 1977 856219	Mean + 2SD	Both	This was defined for each laboratory, with the highest recorded urate value used for calculation. Mean was supposed to be derived from mean SU for a healthy population, depending on the method used. Note colorimetric gives estimates around 17% higher than the uricase method (Higgins 1983)
McCarthy 1991 1747133			Seven patients showed reduced tophi over 10 years with a mean SU of 6.2 in that time, while seven had mean SU of 8.2 and showed increased tophi or unchanged
Smyth 1999 No PMID	6.0 7.0	Women Men	Unclear, mainly just opinion of one man who wrote the chapter
Lin 2000 10782835	6.0 7.0	Women Men	Unknown, could not access full text
	6.6	Women	Conventional criteria (cites Smyth 1999)
Chang 2001 11469473	7.7 6.0 7.0	Men Women Men	Unclear, potentially to allow comparison to other studies
Li-Yu 2001 11296962		Men	9 of 16 patients who had SU below 6 mg/dL for several years showed no evidence of crystals in joint, vs 2 of 16 who did not maintain this SU
Perez-Ruiz 2002 12209479		95% Men	Baseline SU was around 9 mg/dL and was reduced to between 3 and 6 on average, with the greater reductions associated with better improvement in tophus size. It appears that one obtains some reduction even at SU of around 7 mg/dL but it works better at lower concentrations. Note the colorimetric method is probably overestimated urate
Becker 2005 16339094	6.0 8.0	95% Men	Primary end point of clinical trial comparing febuxostat to allopurinol, when measured across three monthly visits it was less common than one-off
			Entry criteria for clinical trial comparing febuxostat to allopurinol
Zhang 2006 16707532	6.0		Saturation point for monosodium urate; goal of ULT is to promote crystal dissolution and prevent crystal formation; this SU level should be maintained for this to have an effect. Shows plot of effect of ULT at different doses with <6 mg/dL only consistently achieved above 600 mg/day. Claims that studies have shown maintenance below 6 reduces tophus burden and depletes crystal burden in joints (McCarthy 1991, Perez-Ruiz 2002 and Li-Yu 2001)
Perez-Ruiz 2007 17907217	6.0	Both	Review article that reiterates most of the papers above, confirming the 6 mg/dL
	5.9	Both	Mean SU was 8.2 mg/dL among those with crystal-proven gout vs 6.05 among those without crystals. Also 89% male in crystal proven vs 62% male in non-crystal proven
Janssens 2010 20625017	5.7 7.1	Women Men	Does not state where these came from

Table 11. Cont.

Publication (Author Year PMID)	Definition SU > mg/dL	Sex	Justification/Notes
Zhu 2011 21800283	5.7	Women	Based on NHANES-III laboratory definition (cites NHANES-III reference manuals and reports CD-ROM). NHANES-III reference manual states normal range is 3.4 to 7.0 for men and 2.4 to 5.7 for women. These were determined by Boehringer Mannheim Diagnostics (BMD) for their Hitachi 737 instrument Widely accepted therapeutic target (cites Becker 2005, Zhang 2006, Perez-Ruiz 2007) Above the supersaturation point No justification (cites Chang 2001)
	7.0	Men	
	6.0	Both	
	7.0	Both	
Chen 2012 21761146	6.6	Women	No justification (cites Chang 2001)
	7.7	Men	
Matsuo 2014 24441388	7.0	Men	No justification
Neogi 2015 26359487	6, 8, or 10	Both	Highest value recorded; should be intercritical (>4 weeks after start of episode); should not be on ULT. Below 4mg/dL loses 4 points, 4–6 = 0 points, 6–8 = 2, 8–10 = 3, 10+ = 4
Chiou 2020 31074584	6.8	Both	Concentration at which urate precipitates into MSU at a physiologic pH regardless of sex (cites Mikuls 2017 textbook chapter, which itself does not cite anything for this)
Haeckel 2020 No PMID			Reports reference intervals of up to 10 mg/dL for both men and women; however, this is age and laboratory dependent. Also shows huge dependence on time of day for measurement, with a 2 mg/dL higher peak around 5 AM. Be a little cautious interpreting this as the text does not match with the figure
Pálinkás 2022 35939175	7.0	Both	No justification

Table 12. Intra-articular temperature estimates.

Publication (Author Year PMID)	Joint	N	Age Range/Mean	Sex	Joint Range/Mean (SD)	Surface Range/Mean (SD)	Urat Solubility	Condition/Notes
Horvath 1949 16695699	Knee	4	32–44	Men	31.4–32.8	29.6–31.9	4.6–5.2	Healthy degenerative arthritis Reiter's syndrome/gout
		7	48–67	Women	33.9–35.3	30.0–33.5	5.6–6.2	
		2	21–36	Men	31.9–35.6	30.8–32.7	4.9–6.4	
	Knee + Elbow	5	18–65	Both	35.0–36.2	32.8–35.0	6.0–6.5	Severe RA
Akerman 1987 3480567	Knee	4	30–61	Men	33.6–33.8	32.1–33.4	5.4–5.5	Moderate RA
		4	50–71	Both	30.0–34.3	29.2–33.3	4.5–5.8	Slight/inactive RA
Weinberger 1989 2711138	TMJ	10	29–40	Both	35.3–37.0	33.9–35.9	6.2–6.9	Healthy
Kim 2002 12402375	Knee				35.2 (1.5)	–	6.1	
Warren 2004 14977671	Knee	20	23–68	Both	33.9 (1.2)	31.8 (1.0)	5.6	Baseline prior to cold treatment
Sánchez-Inchausti 2005 15891720	Knee	12	26	Both	32.5–35.0	27.5–32.0	5.2–6.0	Baseline prior to cold treatment
Becher 2008 18405365	Knee	30	18–72	Both	32.2 (0.3)	–	5.1	Baseline prior to arthroscopy
	Knee	6	27–32	Men	29.7–34.3	25.5–28.0	4.4–5.8	Baseline prior to exercise

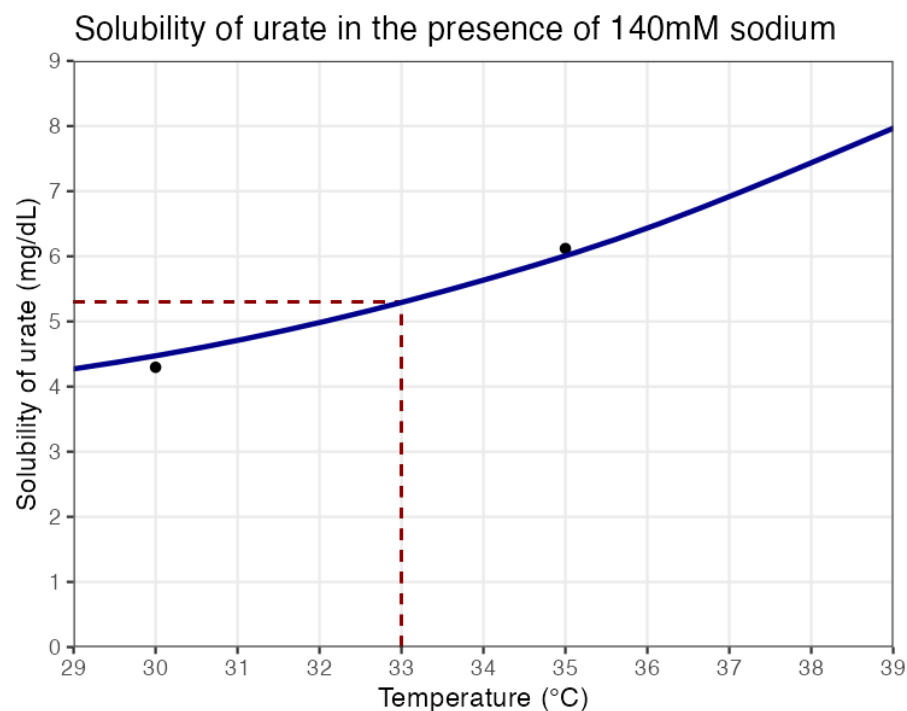


Figure 9. Solubility of urate in the presence of 140 mM sodium. This was derived from the data in Allen 1965, analyzed using the same method as Loeb 1972. The red dashed lines represent the estimated mean intra-articular temperature and corresponding urate solubility estimate.

13. Adherence to the Gout and Crystal Arthritis Network (G-CAN) Consensus Statements for Gout Nomenclature

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Abstract: Background: Uniform terminology with standardized definitions for the various elements and states of a disease ensure accurate and consistent technical communication. In 2019 the Gout and Crystal Arthritis Network (G-CAN) published consensus statements for the nomenclature of disease elements and disease states in gout. The aim of this study was to determine adherence to the G-CAN consensus statements since the G-CAN publication. Methods: ACR and EULAR conference abstracts were searched using online databases for the keywords “gout,” “urate,” “uric acid,” “hyperuricaemia,” “tophus” and/or “tophi” before and after-publication of the consensus statements (1 January 2016–31 December 2017 and 1 January 2020–31 December 2021, respectively). Abstracts were manually searched for labels used to reference gout disease elements and states. Labels were extracted from text, figures and tables. Use of the G-CAN agreed labels, as well as alternatives, were compared between the two time periods and between abstracts that included a G-CAN consensus statement author and those that did not in 2020/2021. Use of the term “chronic gout,” which G-CAN advised should be avoided, was also compared between the two time periods. Results: There were 988 abstracts included in the analysis; 596 in 2016/2017 and 392 in 2020/2021 (Figure 10). G-CAN agreed labels were used in 445/596 (74.9%) of abstracts in 2016/2017, increasing to 311/392 (79.4%) in 2020/2021 ($p = 0.006$). Use of the agreed labels “urate,” “gout flare” and “chronic gouty arthritis” increased between the two

periods. There were 219/383 (57.2%) abstracts with the agreed label “urate” in 2016/2017 compared to 164/232 (70.7%) in 2020/2021 ($p = 0.001$). There were 60/175 (34.3%) abstracts with the agreed label for “gout flare” in 2016/2017 compared with 57/109 (52.3%) in 2020/2021 ($p = 0.003$). Only 1/49 (2.0%) abstract used the agreed label for “chronic gouty arthritis” in 2016/2017 compared to 6/39 (15.4%) in 2020/2021 ($p = 0.022$). Abstracts with consensus statement authors used the correct labels in 87.4% compared to 74.5% without in 2020/2021 ($p < 0.001$). Use of the label “chronic gout” declined between the two time periods. There were 29/49 (59.1%) abstracts in 2016/2017 that used the label “chronic gout” compared with 8/39 (20.5%) abstracts in 2020/2021 ($p \leq 0.001$). Conclusions: Use of the G-CAN agreed gout labels has increased but gout nomenclature remains imprecise. Additional efforts are needed to ensure consistent use of agreed nomenclature for gout in the scientific literature.

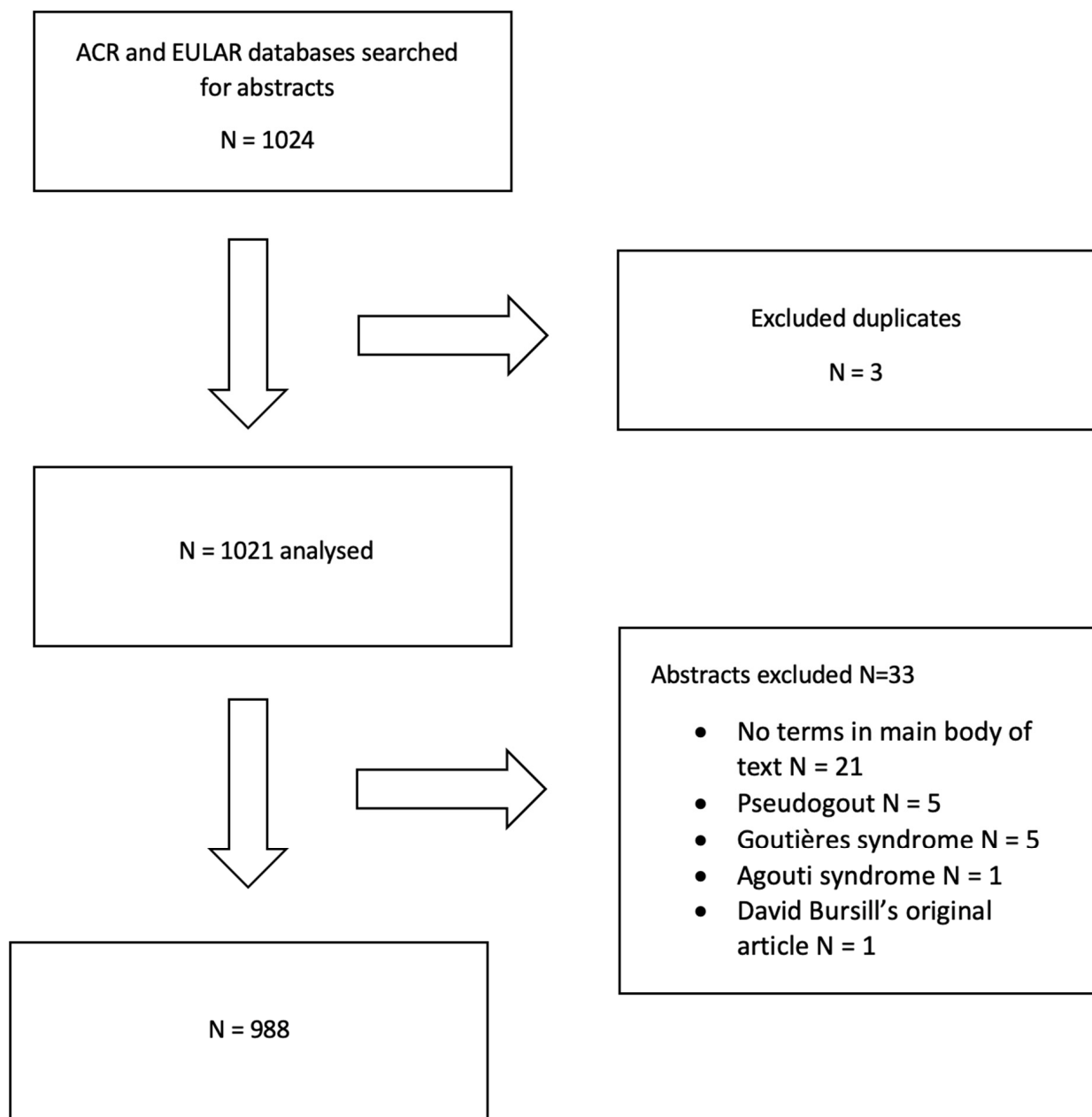


Figure 10. Consort diagram of abstract inclusion criteria.

14. Could the Extent of CPP Deposition Provide Novel Insights in the Pathogenetic Mechanisms of CPPD? Preliminary Results of an Ultrasound Study

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Abstract: Background: The knees and wrists are considered to be the most frequently involved joints in calcium pyrophosphate deposition (CPPD) disease, but to date there is limited evidence regarding the extent of crystal deposition in these sites. Recently the OMERACT ultrasound working group–CPPD subgroup validated a semiquantitative scoring system for assessing CPPD extent, allowing an evaluation of the burden of CPPD. The aim of this study was to assess the extent of CPPD and the frequency of involvement of different anatomical structures in the knees and wrists in different CPPD disease phenotypes. Methods: This was a cross-sectional study conducted between April 2023 and July 2023. Consecutive patients diagnosed with CPPD disease based on the 2023 ACR/EULAR classification criteria were prospectively enrolled. The ultrasonographic assessment was carried out by two rheumatologists expert in CPPD and ultrasound, whose reliability has been tested previously. The OMERACT scoring system for CPPD was used to evaluate the extent of CPPD. Descriptive statistical analyses were performed to analyze the collected data. Results: Twenty-eight patients were enrolled (17 female), with a mean age of 76 years (± 9 SD). The patients were classified into three clinical subsets according to the 2011 EULAR recommendations: 11 had acute CPP crystal arthritis, 13 had chronic CPP crystal inflammatory arthritis and 4 had osteoarthritis with CPPD (Figure 11). In all patients, at least one medial meniscus (MM), one lateral meniscus (LL) and one triangular fibrocartilage complex (TFCC) of the wrist was affected. MM showed the highest bilateral involvement (93% of cases), followed by the LL and TFCC (86% of bilaterality in both cases). No significant differences were found regarding the frequency of involvement of the various sites by subsets of disease. Regarding the extent of deposition, at the patient level, the overall mean score (ranging from 0 to 24) was 14.2 (SD 4.3, median 14). Patients with acute CPP crystal arthritis had a mean score of 13.5 (SD 3.8, median 13), those with chronic CPP crystal inflammatory arthritis had a mean score of 13.8 (SD 4.9, median 13) and patients with osteoarthritis with CPPD had the highest mean score of 17.5 (SD 1.3, median 17.5) (Table 13). At the tissue level, the mean extent of CPPD was 2 (SD 0.8, median 2) at the level of menisci, 1.9 (SD 0.8, median 2) at the TFCC and 1 (SD 0.9, median 1) at the level of the HC. Conclusions: In patients who satisfy the new ACR/EULAR criteria for CPPD disease, at least one wrist and one knee are involved in 100% of patients. These data could reflect some limitations in the ACR/EULAR criteria to capture initial cases with a lower burden of deposition. When analyzing the extent of CPPD according to the 2011 EULAR subsets, a higher load of crystals was found in patients with the subset of OA plus CPPD than in patients with acute CPP flares or with chronic arthritis. These data suggest that release of crystals in joint space (and thus fewer deposits in tissues) in patients with frequent acute or chronic forms of arthritis is a key player in the development of inflammation. Finally, fibrocartilage appears to be more frequently and also more severely involved in CPPD.

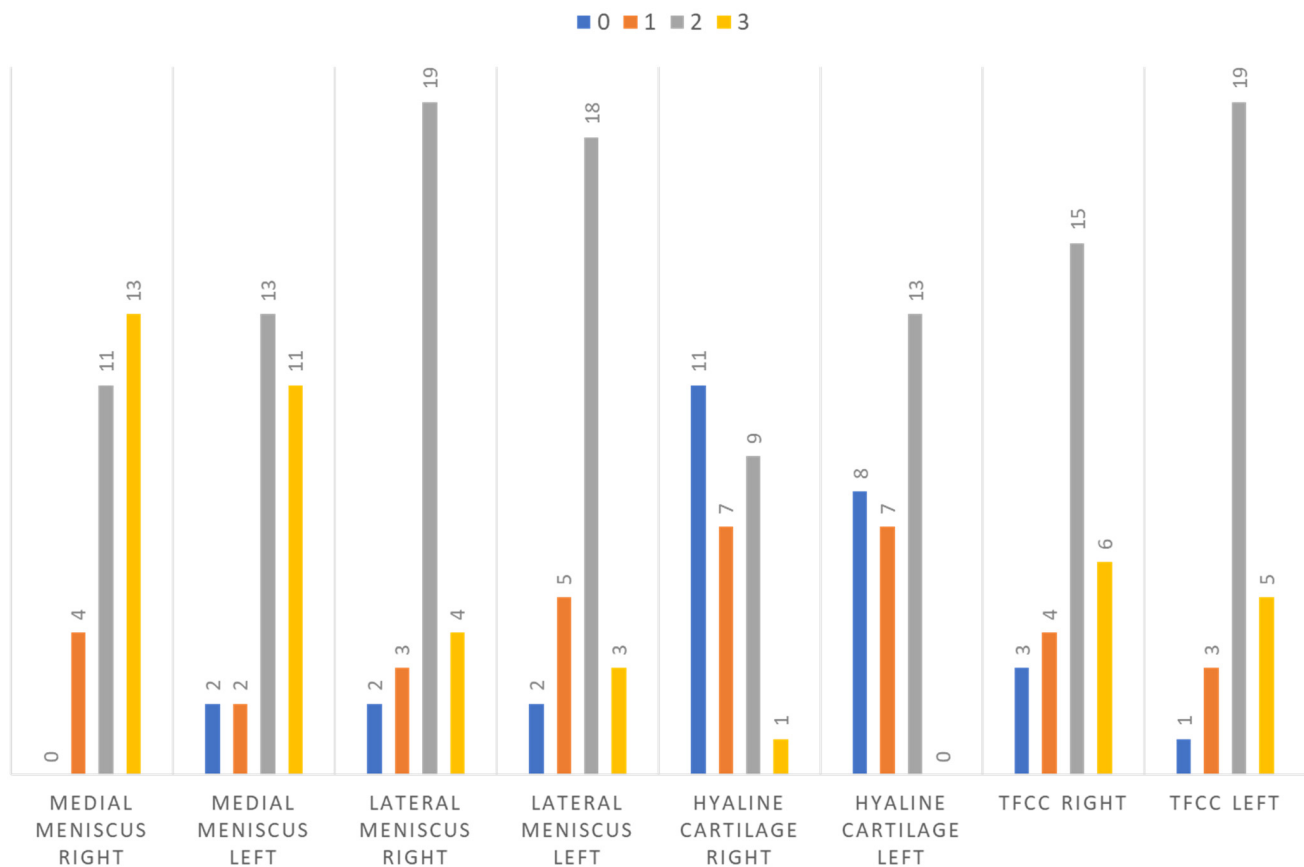


Figure 11. Overall distribution of all the scores (grade 0–1–2–3) in CPPD patients. The values above the bars are number of patients. TFCC, triangular fibrocartilage complex.

Table 13. Score distribution in different CPPD phenotypes.

		0	1	2	3
Acute CPP crystal arthritis (11 pts)	Right MM	0 (0%)	1 (9%)	5 (45.5%)	5 (45.5%)
	Left MM	0 (0%)	0 (0%)	7 (63.6%)	4 (36.4%)
	Right LM	1 (9%)	2 (18%)	8 (73%)	0 (0%)
	Left LM	0 (0%)	3 (27.3%)	8 (73%)	0 (0%)
	Right HC	5 (45.5%)	1 (9%)	5 (45.5%)	0 (0%)
	Left HC	3 (27.3%)	3 (27.3%)	5 (45.5%)	0 (0%)
	Right TFCC	3 (27.3%)	1 (9%)	5 (45.5%)	2 (18.2%)
	Left TFCC	1 (9%)	3 (27.3%)	6 (54.5%)	1 (9%)
Chronic CPP crystal inflammatory arthritis (13 pts)	Right MM	0 (0%)	3 (23.1%)	5 (38.5%)	5 (38.5%)
	Left MM	2 (15.4%)	2 (15.4%)	5 (38.5%)	4 (30.8%)
	Right LM	1 (7.7%)	1 (7.7%)	8 (61.5%)	3 (23.1%)
	Left LM	2 (15.4%)	2 (15.4%)	7 (53.8%)	2 (15.4%)
	Right HC	6 (46.1%)	4 (30.8%)	2 (15.4%)	1 (7.7%)
	Left HC	5 (38.5%)	3 (23.1%)	5 (38.5%)	0 (0%)
	Right TFCC	0 (0%)	3 (23.1%)	7 (53.8%)	3 (23.1%)
	Left TFCC	0 (0%)	0 (0%)	9 (69.2%)	4 (30.8%)
OA with CPPD (4 pts)	Right MM	0 (0%)	0 (0%)	1 (25%)	3 (75%)
	Left MM	0 (0%)	0 (0%)	1 (25%)	3 (75%)
	Right LM	0 (0%)	0 (0%)	3 (75%)	1 (25%)
	Left LM	0 (0%)	0 (0%)	3 (75%)	1 (25%)
	Right HC	0 (0%)	2 (50%)	2 (50%)	0 (0%)
	Left HC	0 (0%)	1 (25%)	3 (75%)	0 (0%)
	Right TFCC	0 (0%)	0 (0%)	3 (75%)	1 (25%)
	Left TFCC	0 (0%)	0 (0%)	4 (100%)	0 (0%)

15. Histological Characterization of Menisci in Patients with Osteoarthritis and Calcium Pyrophosphate Deposition (CPPD)

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Abstract: Background: Calcium crystals, including both basic and pyrophosphate, are frequently observed in patients with osteoarthritis (OA). The processes underlying their formation and their role in OA pathogenesis remain unclear, and basic studies performed on hyaline cartilage (HC) provided partial and in some cases contrasting data. On the other hand, imaging studies demonstrated that fibrocartilage (FC) is at least equally involved in CPPD as HC, but much less is known about the changes of this tissue during the CPPD course. The objective was to use a combined approach from clinical, imaging and histological data from both HC and FC in order to identify potential promoters and mechanisms of calcium crystals formation in joints. In this abstract, we present the preliminary histological findings in menisci of patients with CPPD. Methods: Both menisci of a patient who underwent total knee replacement with CPPD identified at X-rays of the knee and at an advanced stage of osteoarthritis were retrieved during surgery. For conventional light microscopy studies, meniscal specimens were fixed 24h in 10% neutral buffered formalin, dehydrated in a graded ethanol series and cleared with xylene, embedded in paraffin and cut into 4µm sections. Samples were stained with hematoxylin and eosin (H&E) and analyzed. Histological slides were also analyzed by compensated polarized light microscopy to identify the presence of crystalline material. For immunohistochemistry, meniscal slices were treated, after antigen retrieval, for 10 min with 0.1% H₂O₂ and blocked with normal serum. Immunostaining was performed overnight at 4° C with anti-Collagen X (10µg/mL) but in negative controls; detection was performed with a streptavidin-biotin system and diaminobenzidine. Counterstaining of nuclei was performed with Meyer’s hematoxylin. Results: Polarized microscopy shows circumscribed structures filled with rhomboid-shaped crystals, characteristic of CPPD (Figure 12). H&E staining detected the same deposits of CPP crystals (foci) often surrounded by putative hypertrophic chondrocyte clusters. These foci were partially but strongly positive to collagen X, a marker of hypertrophic chondrocytes. Its presence in these structures suggests a role of hypertrophic chondrocytes in the process of formation/deposition of CPP crystals. Conclusions: Although the exact order of different structure involvement in CPPD is not yet known, fibrocartilaginous tissues might play a significant role in the development of both CPPD and OA. These preliminary results raise several questions on the pathogenic mechanisms underlying CPP formation, and further investigation could provide important insights into several processes in both diseases.

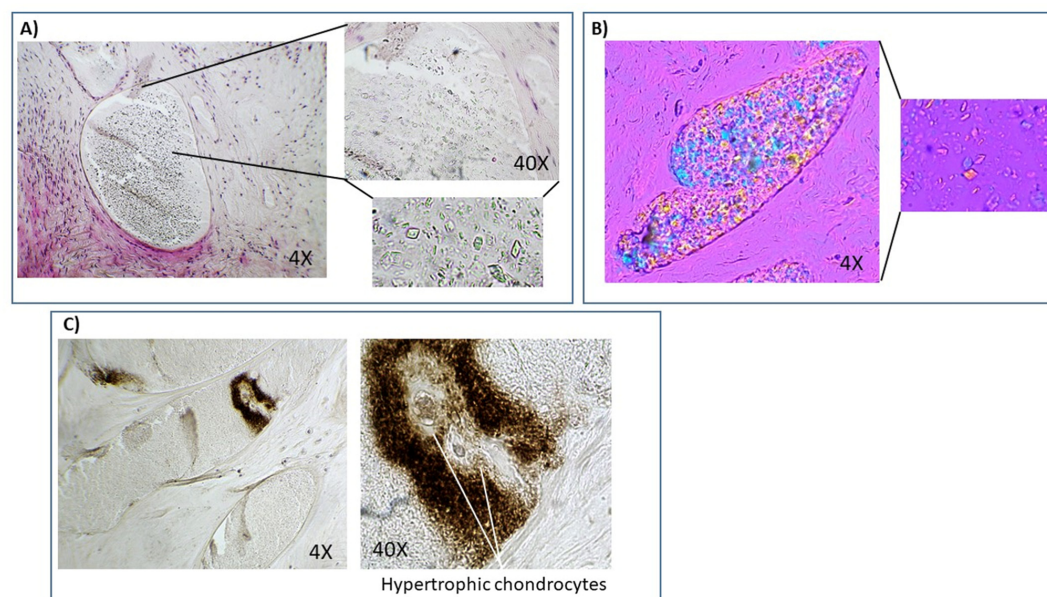


Figure 12. Histopathological features of CPP in meniscus. (A) H&E staining; (B) polarized light microscope analysis; (C) immunohistochemical analysis with collagen-X antibody.

16. The Impact of the 2011 EULAR Recommendations for the Nomenclature of CPPD in the Terminology Used in the Literature

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Abstract: Background: Calcium pyrophosphate deposition (CPPD) disease is a complex nosologic entity that may present with various clinical manifestations, ranging from acute monoarthritis of a large joint to axial inflammatory involvement. Further, calcium pyrophosphate crystals may be found in joints of asymptomatic patients or also in association with other diseases, such as osteoarthritis (OA), making symptom attribution challenging. This complexity has led to a large variety of names for CPPD disease in the past, resulting in several “pseudo-”syndromes, like pseudo-gout, pseudo-rheumatoid arthritis, etc. In 2011, a EULAR task force attempted to mediate this semantic issue by publishing a consensus paper on the nomenclature of CPPD. Here we examine the impact of the 2011 EULAR recommendations on the international literature regarding the terms (labels and acronyms) used to define CPPD and calcium pyrophosphate crystals. Methods: This is an ancillary study of the G-CAN project on the nomenclature for CPPD. In brief, a systematic literature review was carried out in order to extrapolate all labels and acronyms used for CPPD from 2000 to 2022 (included). The articles were then divided into before and after 2011, year of

publication of the recommendations, and the frequencies of the terms suggested by the EULAR taskforce were calculated to assess the impact of the 2021 EULAR terminology. Results: A total of 2376 papers were included in the review, 972 from 2000 to 2011 and 1401 after (4 papers with missing data). Regarding crystal's label and acronym, CPP (calcium pyrophosphate crystals) was used in 12 papers (out of 261 that provided an acronym, 4–5%) and CPPD (calcium pyrophosphate dihydrate) was used in 235 (90%) before 2011 while after publication of the terminology 217 papers (out of 380 who provided an acronym) used the term CPP (57%) and 149 the term CPPD (39%). Regarding the acronym of the disease, the term CPPD as proposed in 2011, defined as all instances of occurrence of CPP deposition including also the asymptomatic form, was used in 6 out of 90 papers that provided an acronym (7%) before 2011 and 24% after (78/324). Conclusions: The 2011 EULAR recommendations on CPPD nomenclature had only a moderate impact on disease label, but they demonstrated a greater influence regarding the acronym used for crystal (CPP). A reason for this could be the lack of an exact definition of the letters of the acronym CPPD in the paper that could be associated with different words, especially regarding the D that could be read as “dehydrate,” “deposition” or even “disease.” It is quite urgent and important to make uniform the terms used to define the disease and its clinical states and to identify strategies that could drive a substantial implementation of these new definitions in research and clinical practice.

17. Peripheral Arterial Disease and Sequelae in Individuals with Gout, Diabetes, or Both: A US Veterans Population-Based Study

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Abstract: Background: Peripheral arterial disease (PAD) causes substantial morbidity and mortality. Patients with gout are known to have increased coronary artery disease risk, but less is known about their risk for PAD. Using electronic medical record data from the national Veterans Health Administration (VHA) system, we examined associations between gout, PAD and PAD sequelae including lower extremity amputation (LEA). We used diabetes (DM), a well-established risk factor for PAD, as a positive comparator. Methods: We collected deidentified data from all VHA patients nationally with an active medical record from 2014 to 2018. After identifying PAD prevalence among all patients, we selected a random sample of 20% for initial analysis to allow for later internal validation. Results: 7,161,715 records were reviewed. In the total population, PAD identified through diagnosis code was 2.2× more prevalent in those with gout alone, 3.2× more prevalent in those with DM without gout and 4× more prevalent in those with gout + DM than those with neither (controls). Amputations by CPT codes yielded similar findings: 2.5× more prevalent in gout alone, 4.2× in DM without gout and 5.8× in gout + DM compared with controls. Patients with gout + DM had the highest mean SU at 8.2 mg/dL (SD 1.8) compared to 7.3 (SD 1.6) in DM only, 7.0 (SD 1.8) in gout only and 6.0 (SD 1.4) in controls. Patients with gout alone had rates of amputations that were higher than controls but lower than those with DM alone. Patients with gout + DM had the highest rates of amputations. After controlling for potential risk factors, those with gout were 1.7× (1.68–1.82) more likely to have PAD. Patients with DM were 2.6× (CI: 2.53–2.63) more likely. Patients with gout + DM were 3.2× (CI: 3.0–3.4) more likely to have PAD. Conclusions: In a national VA cohort, individuals with gout were at significantly greater risk for PAD and LEA than patients without gout but at lesser risk than individuals with DM, even after adjustment for confounders.

18. Gout: A Gateway to Chronic Opioid Use?

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Abstract: Background: Painful gout flares often lead to healthcare visits, which, based on prior reports, result in the use of opioid therapy for management, despite opioids not being a preferred treatment. Opioid use for flares raises concerns that uncontrolled gout may serve as a “gateway” to chronic opioid use. The objectives of this study were to (1) compare the risk of initiating chronic opioid use in Veteran’s Health Administration (VHA) patients with and without gout and (2) to examine determinants of initiating chronic opioid use in gout patients. Methods: We performed a matched cohort study, identifying patients with gout using national VHA data from January 1999 to January 2015 based on ≥ 2 ICD-9 codes for gout (274.X). Gout cases were matched to patients without gout (up to 1:10) based on birth year, sex and VA enrollment year, then followed from the index date (fulfillment of gout algorithm) until the earliest date of incident chronic opioid use, death or 5 years after the index date. Individuals with a fill of an opioid in the year prior to the index date were excluded. Chronic opioid use was defined as 90 cumulative days’ supply with at least two dispenses occurring in a 6-month window with no gap >32 days. Associations of gout (vs. non-gout) with chronic opioid use were quantified using a cumulative hazard curve and multivariable Cox proportional hazards regression. Associations between patient characteristics and time-to-initiating chronic opioid use among patients with gout were examined. Covariates in both models included race, comorbidities, body mass index (BMI) and smoking status. In the gout-only model, additional covariates included age, sex, Rheumatic Disease Comorbidity Index (RDCI), time-varying serum urate (SU) control (average SU <6 mg/dL in prior year) and urate-lowering treatment (ULT; ≥ 2 fills of ULT with ≥ 90 days covered by dispensing in prior year). Results: Over 16.7 million patient-years of follow-up (median follow-up 5 years), 6.9% of gout patients initiated chronic opioids vs. 3.8% of non-gout patients (Figure 13, Table 14). After adjusting for covariates, patients with gout were significantly more likely than non-gout patients to initiate chronic opioid use (aHR 1.36; 95% CI 1.34 to 1.39). Factors associated with gout-related chronic opioid exposure are summarized in Figure 14. Among those with gout, factors positively associated with chronic opioid use included Black/African American race, comorbidities, ULT use and rheumatology encounter. Factors negatively associated with chronic opioid use in those with gout included male sex, CKD, urban residence, SU control, age and Asian, Native Hawaiian/Pacific Islander and American Indian race. Conclusions: In the VHA, we found that patients with gout were 36% more likely than those without gout to initiate chronic opioid use, after accounting for potential confounders, despite opioids not being recommended for management of gout flares. Associations between patient characteristics and time-to-initiating chronic opioid use highlight potential gaps in care, particularly among underserved Black/African American and rural populations as well as the potential for adequate urate control to reduce the risk of chronic opioid use in gout.

Table 14. The frequency, crude rate and hazard ratios of opioid exposure leading to chronic use in patients with gout (vs. non-gout).

	Non-Gout (<i>n</i> = 3,608,182)	Gout (<i>n</i> = 419,837)
Patient initiating chronic opioid use, <i>n</i> (%)	137,497 (3.8)	28,948 (6.9)
Patient years (pt-yrs) of follow-up	14,951,085	1,749,357
Crude rate (95% CI), per 1000 pt-yrs	9.2 (9.1–9.2)	16.5 (16.4–16.7)
Unadjusted HR (95% CI)	Reference	1.78 (1.75–1.80)
Adjusted HR (95% CI) *	Reference	1.36 (1.34–1.39)

* Covariates include age, index year, race (Black/African American, Other or Missing vs. White), BMI, smoking status (Former, Current or Missing vs. Never), chronic lung disease, past myocardial infarction, cardiovascular disease, stroke, hypertension, diabetes, fracture, depression, stomach ulcer or cancer.

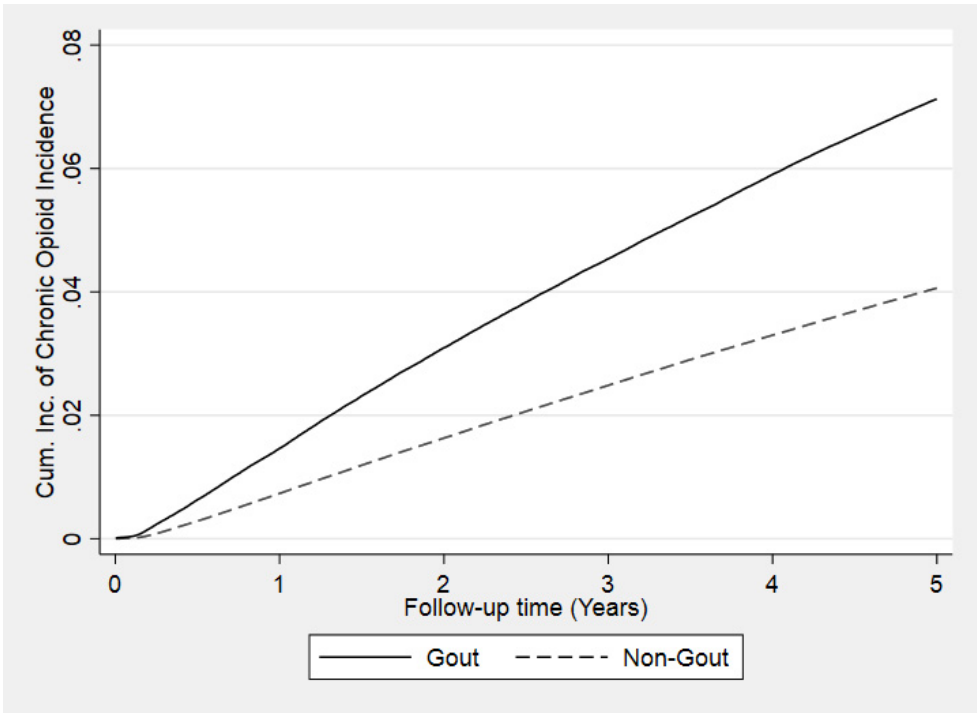


Figure 13. Cumulative hazard of opioid exposure leading to chronic use in patients with gout (vs. non-gout).

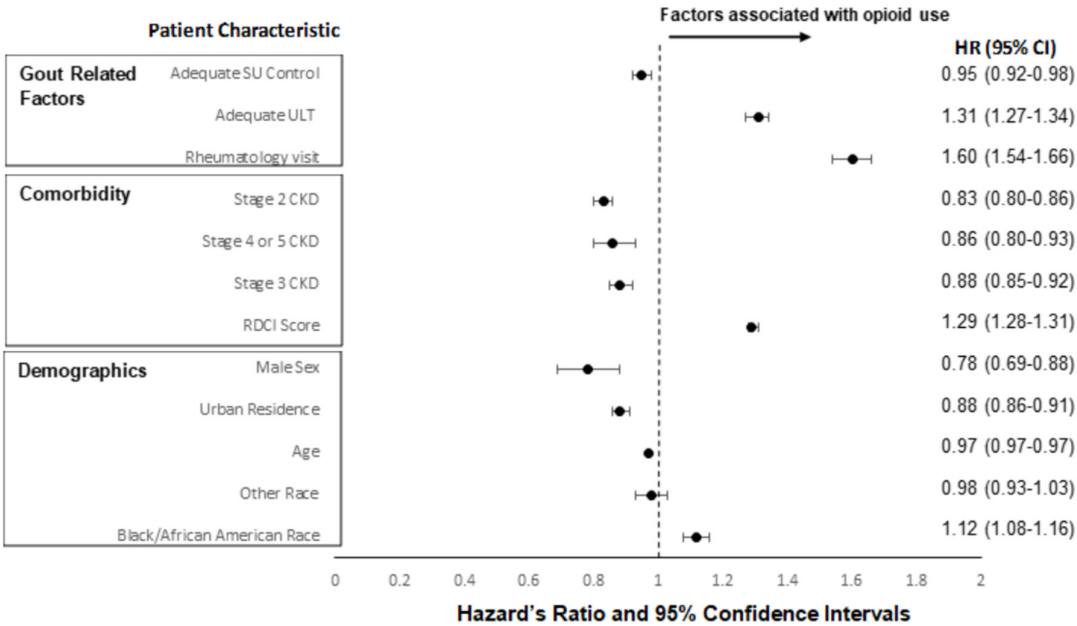


Figure 14. Factors associated with initiating chronic opioid use in patients with gout. *All variables in multivariable model with p -value < 0.05 are shown in the figure. White/Caucasian race was referent value; Other race includes composite of Asian, Native Hawaiian/Pacific Islander and American Indian. Adequate ULT indicates ≥ 2 fills of ULT –AND– at least ≥ 90 days covered by dispensing. Adequate SU control indicates average SU < 6 mg/dL. Age reported in years; Rheumatology visit reported as presence of any visit throughout follow-up period; RDCI (rheumatic disease comorbidity index) including lung disease, myocardial infarction, other cardiovascular disease, stroke, hypertension, fracture, depression, diabetes mellitus, ulcer or stomach problem and cancer. Abbreviations: ULT, urate-lowering therapy; CKD, chronic kidney disease; SU, serum urate.

19. Genetic Colocalization of Gout with Plasma and Urine Metabolites

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Abstract: Objective: To investigate the genetic colocalization of gout-associated genetic loci with genetic control of the metabolome and to investigate the causal role of metabolites in gout. Methods: GWAS data for 1083 plasma metabolites were downloaded [1] and tested for genetic colocalization with gout genetic association data from a recent GWAS [2]. Restricting the locus region to lead SNP $\pm 500\text{kb}$, genetic colocalization analysis was carried out for 276 gout loci (291 independent SNPs) for each of the 1083 metabolite GWAS data using the ‘coloc’ R package. Colocalization occurred if the posterior probability of colocalization was ≥ 0.8 . Ten metabolites with the highest number of loci colocalized with gout were then tested for a causal role in gout by Mendelian randomization (MR) using the ‘MendelianRandomization’ package in R. The inverse variance-weighted (IVW) and weighted median (WM) methods were used to test for causality, and the MR-Egger method was used to test for pleiotropy. Results: Ten metabolites colocalized with gout genetic association signals in at least five loci: urate (positive control), retinol (vitamin A), diacylglycerol, androstenediol disulfate, androsterone sulfate, threonine, glutamine, pyroglutamine, serine and alanine. Four of these metabolites showed evidence of causality for gout in at least one of the MR methods used; urate (IVW-estimate = 1.48, $P_{\text{IVW}} = 6.01 \times 10^{-5}$ and WM-estimate = 1.65, $P_{\text{WM}} = 3.19 \times 10^{-25}$), androsterone sulfate (C, $P_{\text{IVW}} = 7.71 \times 10^{-3}$ and WM-estimate = -0.09 , $P_{\text{WM}} = 5.87 \times 10^{-10}$), diacylglycerol (IVW-estimate = 0.18, $P_{\text{IVW}} = 1.42 \times 10^{-2}$ and WM-estimate = 0.10, $P_{\text{WM}} = 3.96 \times 10^{-5}$) and glutamine (IVW-estimate = -0.03 , $P_{\text{IVW}} = 0.46$ and WM-estimate = -0.08 , $P_{\text{WM}} = 3.95 \times 10^{-3}$). Urate and androsterone sulfate showed evidence of pleiotropy (MR-Egger intercept $P = 2.19 \times 10^{-2}$ and 5.13×10^{-3} , respectively). Conclusions: Diacylglycerol, glutamine and androsterone sulfate showed evidence of causality for gout. There was a positive relationship between risk of gout with diacylglycerol and an inverse relationship with glutamine and androsterone sulfate. Glutamine is involved in the formation of phosphoribosylamine in *de novo* purine biosynthesis, a key precursor molecule of urate synthesis. Furthermore, glutamine can be converted into glutamate via glutaminolysis and fed into the tricarboxylic acid cycle, which produces substrate for trained immunity of innate immune cells [3]. There is increased macrophage responsiveness with loss of diacylglycerol kinase α [4] (an enzyme responsible for converting diacylglycerol into phosphatidic acid), and it has been hypothesized that the abundance of diacylglycerol species causes increased activation of protein kinase C, which in turn contributes to macrophage responsiveness. Androsterone sulfate is a breakdown metabolite of testosterone. How it could play a causal role in gout is not clear, although it could indicate a causal role for testosterone.

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20. Evaluation of Early Life Factors and Future Gout: A Prospective Cohort Study
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Abstract: Objectives: To investigate the association between early life factors and gout. Methods: A prospective cohort of 491,035 participants free of gout at baseline in the UK Biobank. Cox proportional hazards models were used to estimate the association of early life factors including infancy breastfeeding, birthweight, maternal smoking, comparative body size and height at age 10, age at menarche for women and relative age of the first facial hair for men and incident gout. Results: A total of 9075 participants developed gout over a median follow-up time of 12.8 years (IQR: 11.98,13.53) (Table 15). Maternal smoking was related to a 9% higher risk of gout (HR: 1.09 [1.03–1.15], $p = 0.002$), and a shorter stature at age 10 was associated with an 11% higher risk of developing gout (HR: 1.11 [1.04–1.18], $p = 0.001$) (Table 16). No significant group differences were seen in the main analysis of infancy breastfeeding, birthweight, child body size and puberty. Conclusion: Early-life factors including maternal smoking and childhood shorter stature) are associated with a higher risk of midlife gout, and male is the susceptible group.

Table 15. Population characteristics by case-control status.

	Controls	Cases	<i>p</i> Value
Characteristics	N = 481,960	N = 9075	
Age	56.39 ± 8.1	59.52 ± 7.40	<0.001
Gender, n (%)			
Female	269,849 (55.99)	2141 (23.59)	<0.001
Male	212,111 (44.01)	6934 (76.41)	
Ethnicity, n (%)			
White	453,276 (94.05)	8534 (94.04)	0.968
Non-white	28,684 (5.95)	541 (5.96)	
Education, n (%)			
College/University	156,013 (32.37)	2259 (24.89)	<0.001
Other	325,947 (67.63)	6816 (75.11)	
TDI, mean (SD)	−1.30 (3.09)	−1.08 (3.19)	<0.001
Missing	600	13	
BMI (kg/m ²), mean (SD)	27.31 (4.76)	30.13 (5.07)	<0.001
Missing	2954	75	
Smoking Status, n (%)			
Never	264,709 (55.24)	3936 (43.74)	<0.001
Former	163,450 (34.11)	4159 (46.22)	
Current	50,999 (10.64)	904 (10.05)	
Missing	2802	76	
Alcohol Drinking Status, n (%)			
Never	39,309 (8.16)	638 (7.03)	<0.001
Moderate	290,822 (60.34)	3918 (43.17)	
Excessive	151,829 (31.5)	4519 (49.80)	
Diuretics Use, n (%)			
No	471,392 (97.81)	8246 (90.87)	<0.001
Yes	10,568 (2.19)	829 (9.13)	
Urate (umol/L), mean (SD)	304.97 ± 76.72	438.05 ± 86.32	<0.001
Missing	32,117	659	
History of Hyperuricemia, n (%)			
No	431,141 (89.46)	3348 (36.89)	<0.001
Yes	50,819 (10.54)	5727 (63.11)	

Table 15. Cont.

Characteristics	Controls N = 481,960	Cases N = 9075	p Value
History of Hypertension, n (%)			
No	203,795 (42.28)	1761 (19.40)	<0.001
Yes	278,165 (57.72)	7314 (80.60)	
History of Diabetes, n (%)			
No	457,653 (94.96)	8136 (89.65)	<0.001
Yes	24,307 (5.04)	939 (10.35)	
History of Hyperlipidemia, n (%)			
No	263,945 (54.76)	3777 (41.62)	<0.001
Yes	218,015 (45.24)	5298 (58.38)	

Table 16. Cox proportional hazards models for incident gout by early-life factors.

	Model 1		Model 2		Model 3	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Breastfed as a baby						
No	Reference					
Yes	0.94 (0.89–1.00)	0.068	0.96 (0.90–1.03)	0.239	0.94 (0.88–1.01)	0.084
Birthweight (g)						
Birthweight (per 1-SD increase)	1.00 (1.00–1.00)	<0.001	1.00 (1.00–1.00)	<0.001	1.00 (1.00–1.00)	0.329
High (bw ≥ 4000)	0.95 (0.87–1.03)	0.228	0.95 (0.87–1.04)	0.251	0.96 (0.88–1.06)	0.436
Normal (2500 ≤ bw < 4000)	Reference					
Low (1500 ≤ bw < 2500)	1.23 (1.10–1.37)	<0.001	1.20 (1.08–1.35)	0.001	1.08 (0.96–1.22)	0.181
Very low (1000 ≤ bw < 1500)	1.46 (1.07–1.98)	0.016	1.42 (1.04–1.92)	0.026	0.99 (0.72–1.37)	0.963
Extremely low (0 < bw < 1000)	1.42 (0.92–2.18)	0.112	1.35 (0.88–2.08)	0.170	0.85 (0.54–1.34)	0.478
Maternal smoking around birth						
No	Reference					
Yes	1.22 (1.16–1.29)	<0.001	1.22 (1.16–1.28)	<0.001	1.09 (1.03–1.15)	0.002
Comparative height at age 10						
About average	Reference					
Shorter	1.05 (0.99–1.11)	0.112	1.04 (0.98–1.10)	0.248	1.11 (1.04–1.18)	0.001
Taller	1.00 (0.95–1.06)	0.983	0.98 (0.93–1.03)	0.436	1.04 (0.98–1.10)	0.237
Comparative weight at age 10						
About average	Reference					
Thinner	1.06 (1.01–1.11)	0.031	1.05 (1.00–1.11)	0.025	1.00 (0.94–1.05)	0.890
Plumper	1.34 (1.26–1.43)	<0.001	1.34 (1.25–1.42)	<0.001	1.05 (0.99–1.13)	0.127
Relative age of first facial hair						
About average	Reference					
Younger than average age	1.19 (1.07–1.31)	0.001	1.16 (1.05–1.29)	0.004	1.10 (0.99–1.22)	0.093
Older than average age	0.89 (0.82–0.97)	0.006	0.87 (0.80–0.95)	0.002	0.96 (0.87–1.04)	0.318
Age at menarche						
Menarche (per year increase)	0.97 (0.94–0.99)	0.017	0.96 (0.93–0.99)	0.010	1.01 (0.98–1.05)	0.380
12–14	Reference					
≤12	1.15 (1.04–1.28)	0.006	1.14 (1.03–1.27)	0.012	1.00 (0.89–1.12)	0.981
>14	1.11 (0.97–1.26)	0.134	1.06 (0.92–1.21)	0.426	1.11 (0.96–1.28)	0.172

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