gout, urate, and crystal deposition disease

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Conference Report

14th European Crystal Network (ECN) Workshop—Abstract Proceedings

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Abstract: The 14th annual international European Crystal Network was held in Paris on 2 and 3 March 2023. This in-person meeting was attended by 93 participants. Over 40 research abstract submissions were received from investigators, ranging from early career investigators to senior researchers, for plenary oral and poster presentations. Here, we present the accepted, lightly edited abstracts from the presenters consenting to have their work published. We thank and congratulate the presenters for their work and contributions to the meeting.

Keywords: European Crystal Network; ECN; workshop; gout; CPP deposition disease; recommendations; imaging; genetics; macrophages; innate immunity

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1. Introduction

For 14 years, the ECN workshop has been held in central Paris, apart from 2 years in which we moved to digital meetings due to the COVID-19 pandemic. 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.

This year, we returned to our usual 2-day face-to-face meeting with 93 colleagues of all ages from a variety of countries (Figure 1). Indeed, attendees came from Europe, the USA, Oceania, and Asia.

Thanks to the Scientific Committee, we received 43 abstracts and selected 23 oral communications and 20 posters presented in two sessions.

Ten years after our last report [1], we have the chance, thanks to our partner US G-CAN (Gout, Hyperuricemia and Crystal-Associated Network) group, to report these abstracts in this second issue of the Gout, Urate, and Crystal Deposition Disease (GUCDD), the G-CAN society journal. Only abstracts with permission from their first and/or senior authors are presented.

Among 23 oral communications the highest rated abstract was named as the 2023 ECN Prize: Lukas NOLLET, PhD student from Ghent, Belgium, was our 2023 Winner.

The title of his work is: "Activation of the autotaxin-Lysophosphatidic acid receptor pathway contributes to the pathogenesis of pseudoxanthoma elasticum, a Mendelian ectopic calcification disorder". He will be invited next year to the 15th ECN Workshop.

Past 2022 ECN Prize Winner, Victoria HALPERIN KUHNS from Baltimore, United States, attended, and her work, entitled "Source of hyperuricemia drives significantly divergent transcriptional segment specific alterations in the kidney", was also selected for an oral communication.

As usual, we divided our two-day meeting into a half day for calcium-crystal-related diseases—osteoarthritis, CNS diseases, and X-linked hypophosphatemia/Hyp mice. Thursday afternoon was devoted to urate and calcium-crystal-induced inflammation, with variations in disease according to macrophage responses, as well as urate-mediated DNA methylation. Prof Abhishek Abhishek presented, on behalf of the ACR/EULAR task force, the new ACR/EULAR classification criteria for CPP deposition disease after more than 3 years of hard work, both in face-to-face and digital meetings.

On Friday, "the Gout day", we had 2023 updates on the genetics of hyperuricemia with Prof Dr Anna Köttgen, Freiburg, Germany, and the presentation by Prof Tony Merriman of the overall results of a genome-wide association analysis of 2,622,830 individuals revealing new pathogenic pathways in gout. This mega-GWAS was launched in Paris during and after the 3rd ECN workshop by Alex So and Tony Merriman, and has evolved over the years from Euro-GOUT to Global-Gout, along with many other large data sets.

ABCG2, the gene coding for a urate transporter in the gut and the kidney, was also an important subject discussed during the meeting.

Therapeutics were addressed first with allopurinol and two questions—anti-inflammatory effects of allopurinol and cardiovascular outcomes on one hand, and dialysis for the most severe cases on the other hand. Finally, gout management is not only a matter of drug choice, but also of care delivery in order to reduce clinical or therapeutic inertia [2–4]. As an example, nurse-led management has been shown to be an outstanding type of care delivery for gout patients, reaching far better outcomes than general practitioners [5,6]. A second preliminary communication reported on imaging EULAR recommendations for crystal-induced arthropathies [7–9].

We hope you will enjoy this set of 10 abstracts.

We are already preparing the 15th ECN workshop, Paris, 7–8 March 2024: save the date and keep checking the ECN Website (www.european-crystal-network.com (accessed on 3 March 2024)) for updated information.

Figure 1. Attendees of the 14th ECN workshop.

Scientific Committee 2023 (alphabetic order): Prof. Jessica Bertrand (GE), Prof Nathalie Busso (SW), Dr Tania Crisan (RO), Dr Sonia Nasi (SW), Prof (Emeritus) Michael Doherty (UK), Prof Hyon Choi (USA), Prof (Emeritus) Michael Doherty (UK), Prof Hang-Korng Ea (FR), Prof Leo Joosten (NT), Dr Hervé Kempf (FR), Prof (Emeritus) Frédéric Lioté (FR), Prof Tony Merriman (NZ/USA), Prof Tristan Pascart (FR), Prof Fernando Perez-Ruiz (SP), Prof (Emeritus) Alexander So (SW), Prof (Emeritus) Robert Terkeltaub (USA).

Organizing Committee 2023: Mrs Véronique Gordin (medic-evenement, FR), Prof Hang-Korng Ea (FR), Prof Frédéric Lioté (FR), Prof Tristan Pascart (FR), Prof Fernando Perez-Ruiz (SP), Prof Alexander So (SW).

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2. Investigator-Initiated Pilot Study Evaluating the Efficacy of Etanercept in Acute Gout Flares

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Abstract: Objectives: This study aimed to demonstrate that targeting tumor necrosis factor (TNF) using etanercept 50 mg subcutaneous injection is efficacious for gout flares. Methods: The study was designed as a pilot 14-day, randomized, double-blind study comparing etanercept 50 mg subcutaneous to triamcinolone (TA) 40 mg intramuscular injections for flares. It aimed to show that patients treated with etanercept do not have worse pain at 72 h compared with TA. Statistical analysis—means of continuous variables between arms were compared via Student's *t*-test or Wilcoxon rank-sum test. Results: COVID-19 dramatically impacted the study. Five patients were enrolled and randomized before the sponsor terminated the study early due to the pandemic. All five patients were male, ages: 28–55. Two patients were randomly assigned to the TA arm, and three were assigned to the etanercept arm. The mean baseline VAS in the TA arm was 6, and in the etanercept arm it was 7.7. The mean VAS at 72 h in the TA arm was 1.5, and in the etanercept arm it was 4 ($p = 1$). All four patients completing the study, regardless of the assigned arm, experienced statistically less pain on day 7 ($p = 0.035$) and 14 ($p = 0.018$) compared with day 0. Baseline CRP levels decreased by day 7 ($p = 0.0098$). Conclusion: Etanercept provided equivalent pain relief as compared with TA at 72 h. TA and etanercept-treated patients experienced less pain by day seven, regardless of the assigned arm ($p = 0.035$). Etanercept may be effective for gout flares when conventional therapy is unsuitable or ineffective. Larger studies are warranted.

3. Distribution and Significance of XDH in Various Species

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Abstract: We have studied xanthine dehydrogenases (XDHs) for more than 50 years, including their main distribution and physiological significance and their molecular properties. Initially, we investigated the reaction and regulation of urate formation in chickens, which are urate-excreting animals. For birds, the metabolic significance of removing amino acid amino groups and their purine metabolism was imagined. Studies on the inducibility of the enzyme by the protein content of the diet have confirmed that it is due to the metabolism of amino nitrogen. However, even in the same bird species, the distribution of XDH differed between chickens and pigeons. The XDH molecules were similar in terms of the presence of a sulfur atom in their active center, but they did not convert from XDH to XO. The Mo-S sulfur atom required for activity was essential and varied in content. However, the RC bacterium XDH is Mo-S stable. It was also found that the effect of XDH inhibitors was not inhibitory, except for allopurinol, and this was due to differences in the dynamic structure

of the active site protein. The biological significance of these findings is summarized. Finally, the biological relevance of only mammals changing from XDH to XO is discussed.

4. Effects of De Novo Calcification in a New Ex Vivo Human Model of Osteoarthritis

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Abstract: Background: The pathologic calcification (PC) of cartilage is a hallmark of osteoarthritis (OA). Calcification is a complex biological process initiated by chondrocytes, the only cells present in cartilage. Calcification is represented by the deposition of calcium-containing crystals, encompassing BCP (basic calcium phosphate) and CPPD (calcium pyrophosphate dihydrate) crystals. Objectives: To set-up a new ex vivo human model of OA to evaluate the effects of ongoing cartilage calcification. Methods: Explants from femoral and tibial cartilage obtained from 11 OA patients on the day of knee replacement surgery were cultured with medium alone (DMEM high-glucose, control, NT) or medium supplemented with ascorbic acid and β-glycerophosphate (calcifying medium, CM). CT-scan analysis of the explants was performed on the day of explant isolation (day 0) and after 21 days in culture (T21). Histological analysis of the explants was performed on day 21 using Safranin-O staining. In explant supernatants, IL-6, MMP-3, -13 were measured by ELISA, and glycosaminoglycans (GAG) were analyzed by dimethyl-methylene blue staining. Primary human OA chondrocytes from three independent OA patients were cultured in control medium or calcifying medium. Crystals were identified by RAMAN spectrometry. Results: We found small calcifications at the onset of the experiment (day 0), which increased significantly in the CM group at day 21 (CT scan bone volume day 0 = 1, day 21 = 1.43, N = 11 patients), while there was no increase in the NT group (CT scan bone volume day 0 = 1, day 21 = 1.09, N = 11). Crystals were mainly localized in the cartilage superficial layer, as evidenced by CT-scan and Alizarin-red staining of histological sections of explants at day 21. We reproduced the pro-calcifying effect of CM in isolated OA chondrocytes and assessed by Raman spectrometry that hydroxyapatite crystals were formed under this condition. Similar percentages of apoptotic chondrocytes (NT = 72 $\pm$ 13% versus CM = 77 $\pm$ 9%) were found in explants cultured in NT or CM, ruling out apoptosis as a calcification trigger in this model. We next examined IL-6 secretion by NT and CM-treated cartilage explants. On both days 10 and 21, IL-6 was significantly increased in CM (day 10: 6 $\pm$ 5 pg/mg tissue in the NT group versus 11 $\pm$ 8 pg/mg tissue in the CM group; day 21: 18 $\pm$ 14 pg/mg tissue in NTrt versus 24 $\pm$ 16 pg/mg tissue in CM), further stressing the importance of this cytokine in calcification. Similarly, using primary OA chondrocytes, we also found that CM increased IL-6 secretion. We next asked whether CM could impact cartilage structure. Histological examination of cartilage explant sections stained by Safranin-O revealed a loss of proteoglycans (loss of Safranin-O staining) in CM-treated tissues. In agreement with this latter result, the GAG content was increased in supernatants of CM-treated tissues. We hypothesized that these effects could be accounted for by increased metalloprotease production such as MMP-3 and -13. Indeed, we found increased means of both MMP-3 and -13 in CM-treated explants, although these increases did not reach significance. Using primary OA chondrocytes, we also found that CM significantly increased MMP-13 secretion. Conclusion: Here, we described a new model to study de novo cartilage calcification. We showed that these new calcifications increased IL-6 secretion and had deleterious effects on the cartilage proteoglycans content. This new model will enable the identification of new drugs that could prevent or reduce cartilage calcification in OA.

5. Antinuclear Antibodies in Gout: The New Vomit (Victims of Modern Immunology Techniques)

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Abstract: Non-rational prescriptions of examinations in clinical practice may induce inefficient performances, misdiagnosis, and inappropriate consultations. We analyzed the prescription and results of antinuclear antibody (ANA) prescription before first consultation to a rheumatology unit in a disease with commonly high diagnostic accuracy based on clinical findings of gout. From 2013 onwards, prescriptions and results of ANA testing prior to first rheumatology visits were added to the database, along with general data and variables related to comorbid conditions and clinical characteristics of gout. We performed an analysis of variables plausibly associated with ANA prescription and biennial changes through to the rate of prescription. From 2013 to 2022, 504 patients gave written consent for data inclusion, 66 (13.7%) women and 415 men (86.3%), with a mean age at admittance to the cohort of 73 $\pm$ 14 and 65 $\pm$ 14 years, respectively. ANAs had been prescribed to 114 (23.7%) subjects, in 28/66 (42.4%) women and 86/415 men ($p < 0.001$). No differences for prescription were observed in other variables, such as age, time from onset, flares per year, tophi, or polyarticular distribution. The rate of ANA prescription was not related to diagnostics for derivation: arthralgia (24.4%), arthritis (21.7%) or gout (25.3%). In total, 31/114 (27.2%) ANA tests were positive (90% with title < 1/400), but only led to a new diagnosis (autoimmune hepatitis), and two had a previous diagnosis (Sjögren's Syndrome and Systemic Lupus). The rate of positive ANA was much higher in women (12/28, 42.9%) than in men (8/86, 22.1%). The rate of ANA prescriptions showed a biennial and significative increase during the last decade ($p = 0.007$): 11.3% in 2013–2014, 21.4% in 2015–2016, 34.9% in 2016–202017, and 31.1% in 2021–2022. A decline in ANA prescriptions was observed during the SARS-CoV-2 pandemic, between 2019 and 2020 (19.7%). In a disease with quite typical clinical presentation as gout is, the rate of ANA prescription prior to rheumatology consultation is high, and especially high in women, despite old age and the absence of a systemic clinic. The rate of positive ANA testing is quite high, close to 50% in women, and may lead to misdiagnosis and inefficient management: the new VOMIT.

6. Factors Associated to Loss for Follow-Up in a Prospective Gout Cohort

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Abstract: Background: Adherence to treatment has been widely studied, but not adherence to follow-up visits. Objective: To analyze factors associated with loss for follow-up in patients with gout and with a programmed follow-up visit to the rheumatology office. Method: Analysis of data from an inception cohort of patients with gout prospectively followed-up in a university hospital setting. Variables included general data, along with clinical characteristics of gout, comorbidities, treatment, and adherence to prescribed urate-lowering therapy (ULT). Those variables associated ($p < 0.20$) in the bivariate analysis were included in a multivariate analysis. Patients who did not attend a visit because they had passed away were not considered as lost for follow-up. Results: From a series of 1,442 consecutive patients, 354 (24.5%) were lost for follow-up; 219 (15.2%) did not attend because they had died between programmed visits. The mean follow-up until lost for follow-up was 32 months vs. 49 months for patients who remained in active follow-up. Age (older), gender (women), pooled comorbidity (higher), severity of gout (monoarticular), alcohol intake (<15 g/day), adherence (MPR > 80%), previous treatment (none), and consultation (primary care), were associated with higher rates of loss for follow-

up in the bivariate analysis. No association was found between persistence in follow-up and time from the onset of gout, presence of tophi, number of flares per year, or previous and prescribed ULT. In multivariate analysis (Table 1), only higher age, higher adherence to prescribed medication, and consultation from primary care were independently associated with persistence on follow-up. Severity of gout (polyarticular disease) also seemed to be associated with persistence, but this lacked statistical significance. Conclusion: In our clinical setting, the profile of patients at higher risk of abandoning prescribed follow-up is that of younger, poorly adherent, with lower burden of disease, and consulting through an assistance "short-cut" (other than primary care).

Table 1. Multivariate analysis of factors associated with loss for follow-up.

	B	Sig.	Exp (B)	95% C.I.L. for EXP (B)	
				Lower	Upper
Age (year)	−0.029	0.001	0.972	0.955	0.989
Primary care consultation	−1.651	0.008	0.192	0.057	0.647
Adherence (MPR > 0.8)	−1.120	0.000	0.326	0.186	0.572
Severity (polyarticular)	−0.358	0.107	0.699	0.416	0.117
Highest comorbidity (Kaiser 3–4)	0.199	0.519	1.220	0.666	2.234
Previous ULT (none)	−0.196	0.477	1.217	0.709	2.089
Gender (male)	0.256	0.566	1.292	0.539	0.988
Ethanol > 15 g/day	0.005	0.987	0.995	0.543	1.823

7. Rationale and Design for Podagra II: A Multicenter Randomized Phase 2/3 Study Assessing the Efficacy and Safety of Dapansutrile, an Orally Administered Specific Inhibitor of the NLRP3 Inflammasome in Subjects with an Acute Gout Flare

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Abstract: Background: The formation of the NOD-, LRR-, and pyrin-containing 3 (NLRP3) inflammasome plays a critical role in the initiation of the inflammatory reaction induced by monosodium urate (MSU) crystals in an acute gout flare. Once assembled, the NLRP3 inflammasome converts pro-interleukin-1β into its active form and initiates IL-1β-dependent inflammation. NLRP3 activation, therefore, occurs upstream of IL-1β, the pivotal cytokine in gouty inflammation and the causative agent mediating the symptoms of acute gout flares, including joint pain due to inflammation. Monoclonal antibodies against IL-1β can decrease inflammatory pain by the removal of IL-1 β from circulation and shutting down the IL-1β-mediated inflammatory cascade. However, they must be injected and are associated with immune suppression and an increased risk of infection. There remains an unmet need for an orally administered treatment of acute gout to safely reduce IL-1β-mediated inflammatory pain without the risk of immunosuppression. In an initial dose-range finding study, PODAGRA I, we reported preliminary evidence of the efficacy and safety in this setting with dapansutrile, an orally administered specific inhibitor of the NLRP3 inflammasome. **Objectives:** The PODAGRA II study is designed to further evaluate the effects of dapansutrile on reducing acute gout joint pain and IL-1β-dependent inflammation. **Methods:** The study (NCT05658575/EudraCT 2019-002717-19) is a multicenter, placebo-controlled, prospective, randomized, double-blind trial conducted in the Netherlands, Spain, France, and the USA. In total, 300 patients with acute symptomatic gout flare are being randomized centrally to receive either dapansutrile (2000 mg loading dose followed by 1000 mg BID) or matching placebo tablets for 7 days (2:1 ratio dapansutrile: placebo). The study is designed to determine the superiority of dapansutrile compared with a placebo on the symptoms and signs of an acute gout flare. The primary endpoint is the subject-reported pain intensity

score in the target joint (evaluated on a 100 mm visual analogue scale) at 72 h. Secondary endpoints include patient and investigator assessments of response to treatment and the investigator-assessed scores for joint tenderness, swelling, erythema, warmth, and range of motion. A subject-assessed quality-of-life questionnaire will be collected, and biomarkers associated with acute gout inflammation (IL-1 β, IL-6, and CRP) will be evaluated. In order to demonstrate both statistical and clinical significance, approximately 170 and 85 evaluable subjects are needed in the dapansutrile and placebo arms, respectively. This assumes a one-sided significance level of $\alpha = 0.025$, 85% power (1-β), a standard deviation of 25 points, and an expected mean difference ($\delta = 10$ points) plus an additional clinical significance of $\delta = 10$ points. To account for dropouts and non-evaluable subjects, up to 200 subjects in the dapansutrile arm and up to 100 in the placebo arm will be randomized. **Results:** The trial has been launched and is currently enrolling subjects. **Conclusion**: PODAGRA II will be the first placebo-controlled, adequately powered, large, multi-center study with dapansutrile, an oral NLRP3-specific inhibitor. Gout is a prototypical disease of NLRP3 activation; therefore, this trial will provide important new data on NLRP3 inhibition leading to a reduction in joint pain and associations with acute gout flares.

8. Which Is the Most Appropriate Sonographic Definition for Asymptomatic Hyperuricemia with MSU Crystal Deposits?

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Abstract: Background: Cumulative data indicate that 20–30% of subjects with asymptomatic hyperuricemia (AH) have silent monosodium urate (MSU) crystal deposition [1]. For its evaluation, several sonographic examination schemes have been used [2], and the scanning of the first metatarsophalangeal (MTP) joint and femoral condyle for double contour (DC) sign, plus the first MTP for tophi, shows the highest prevalence and discrimination compared with subjects with normouricemia. However, how we should sonographically classify AH with crystal deposits remains to be defined. **Aim:** To compare the variation in the prevalence of sonographic deposits in AH across different classification schemes. **Methods**: Observational, cross-sectional study. Patients with AH were consecutively recruited from clinics and wards of internal medicine, cardiology, nephrology, endocrinology, rheumatology, and primary care units in an academic center. Subjects with a recent serum urate level ≥ 7 mg/dL were included, excluding those under urate-lowering therapy and/or colchicine or with gout or another inflammatory rheumatic disease. Ultrasound was performed by an expert rheumatologist sonographer, blinded to clinical and laboratory data, following 2021 OMERACT definitions for elementary gout lesions (DC sign, tophi, aggregates) and 0–3 grading [3]. The locations scanned bilaterally were knees with patellar tendons, ankles with Achilles' tendons, and first and second MTP joints. We applied different definitions for AH with deposits, varying in relation to deposits (any deposits; only DC sign and/or tophi; only grade 2–3 deposits; only grade 2–3 DC sign and/or tophi) or locations (10 locations; reduced 4-joint scheme including knees and 1 MTPs; more than 1 location with deposits). Comparisons were performed through chi-squared tests. **Results**: In total, 77 participants with AH were studied: 55 males (71.4%), with a mean age of 59.8 years (SD 17.3). The mean body mass index was 31.2 kg/m^2 (SD 5.2), and 37.66% and 29.9% suffered from cardiovascular and chronic kidney disease, respectively. Mean uricemia was 7.6 mg/dL (SD 1.6), with a fractional excretion of uric acid of 5.6% (DS 2.2). Regarding the elementary lesions, the median (p25–75) number of locations with DC sign, tophi, or aggregates was 0 (0–1), 1 (0–2), and 1 (1–2), respectively. For grade 2–3 lesions, the numbers were 0 (0–0), 1 (0–1), and 1 (0–2), respectively. The proportions of sonographic deposits largely varied according to the different classifications considered to define AH with deposits, ranging from 23.38% up to 87.01% in a significant manner

($p < 0.050$). **Conclusion**: In a multidisciplinary sample of AH, the rates of sonographic deposits dramatically varied across the different classifications used, highlighting the need for an agreed and validated definition that facilitates further research in this setting.

9. Hyperuricemia Is Associated with Coronary Artery Atherosclerosis in Men: Results from the SCAPIS Study

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Abstract: Background: There is considerable controversy on whether elevated urate levels are independently associated with the development of cardiovascular disease (CVD). Segment involvement score (SIS), as a marker of subclinical atherosclerosis, represents the total number of coronary segments with atherosclerotic plaque, calcified and/or non-calcified, and thus reflects the overall burden of coronary atherosclerosis. The extent of coronary artery disease as quantified by SIS is a strong, independent predictor of cardiovascular events (1). Whether urate levels are associated with SIS has not previously been studied. **Objectives:** To study the association between hyperuricemia and SIS in participants of the Swedish Cardiopulmonary Bioimage Study (SCAPIS). **Methodology:** SCAPIS is a nationwide, population-based study aiming to improve CVD risk prediction. The study included randomly selected individuals aged 50–64 years recruited at six university hospitals in Sweden during the period 2013–2018 (N = 30,000 participants). We used data from SCAPIS Gothenburg (N = 4949 participants), including urate levels and SIS, measured by computed tomography angiography (CTA). Individuals with known coronary heart disease and/or gout were excluded. Hyperuricemia was defined as urate levels $\geq$ 405 µmol/L. The association between hyperuricemia and SIS was assessed by multivariate logistic regression analysis. We calculated odds ratios (OR) and 95% confidence intervals (CI), both crude and with adjustments for age, smoking, body mass index (BMI), diabetes, dyslipidemia, and hypertension. An SIS > 0 was considered to indicate the presence of coronary atherosclerosis, and was used as the cutoff value. **Results:** In total, 2438 men (mean age, 57.3 years) and 2511 women (mean age, 57.4 years) were included. Urate levels were higher in men than in women (mean levels, 348 vs. 270 µmol/L, respectively). Hyperuricemia was more common in men than in women (18% vs. 2%). Age, BMI, and hypertension showed no differences between men and women, while diabetes and dyslipidemia were more common in men than in women (4% vs. 2% and 13% vs. 9%, respectively). Any CTA-detected atherosclerosis (SIS > 0) was found in 1404 (57.6%) men and 752 (30%) women. Hyperuricemia was significantly associated with SIS > 0 in men (OR, 1.3; 95% CI, 1.04–1.6), but not in women (OR, 1.3; 95% CI, 0.7–2.3) in the multivariate logistic regression analysis (Table 2). **Conclusions:** Hyperuricemia was independently associated with the presence of coronary artery atherosclerosis, as reflected by the SIS, in men but not in women. The findings are compatible with the pathophysiological role of urate in atherosclerosis. Whether the observed difference between sexes reflects biological differences in effect of urate or is explained by other factors, such as later onset of atherosclerosis or less statistical power in women, will be examined in follow-up studies.

Table 2. Association between hyperuricemia and coronary artery atherosclerosis, defined as SIS > 0.

Urate Levels, µmol/L	Men N = 2438				Women N = 2511			
	Unadjusted OR (95% CI)	*p*-Value	Adjusted OR * (95% CI)	*p*-Value	Unadjusted OR (95% CI)	*p*-Value	Adjusted OR * (95% CI)	*p*-Value
<404, ref	1		1		1		1	
≥405	1.5 (1.2–1.9)	0.0002	1.3 (1.04–1.6)	0.02	2.2 (1.3–3.8)	0.003	1.3 (0.7–2.3)	0.4

* Adjusted for age, smoking, body mass index, diabetes, dyslipidemia, and hypertension; SIS, segment involvement score; OR, odds ratio; CI, confidence interval.

10. Source of Hyperuricemia Drives Significantly Divergent Transcriptional Segment Specific Alterations in the Kidney

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Abstract: Hyperuricemia (HU) contributes to the development of gout, kidney stones, and kidney disease. Many studies exploring the effects of HU on renal disease progression have yielded inconsistent results based on assumptions that all types of HU have the same pathophysiological outcomes. Here, we compare the effects of underexcretion (UX) vs. overproduction (OP) types of HU on renal gene expression in each nephron segment to provide insight into how HU may impact kidney disease. Both types of HU result in similar serum urate levels, but critically important differences in renal urate handling with disparate tubular urate levels. Our ABCG2 knock-in UX model (Q140K) has decreased urate secretion, with increased serum urate in male mice only; our OP model is a novel inducible knock-out of the urate metabolizing gene uricase (UOX-iKO), which renders mice unable to metabolize urate, increasing circulating urate levels. UOX-iKO male mice were induced at 9 weeks old. Mice had elevated serum urate levels similar to age-matched Q140K male mice from 2 weeks to 6 months after induction. RNA-seq was performed on kidneys harvested from HU male animals from both models and controls, followed by DESeq2 differential expression analysis. Using published RNA-seq data from micro-dissected nephron segments, gene lists were compiled to create renal-segment-specific transcriptional profiles. Differentially expressed genes (DEGs) from both models were compared with segment-specific profiles to determine which regions of the kidney were most enriched. UOX-iKO mice exhibited increased overall urinary urate excretion (UUE) and increased fractional excretion of urate (FEU), consistent with urate OP. In contrast, Q140K mice showed no change in UUE and decreased FEU, consistent with urate UX. The two models of HU showed significantly divergent transcription profiles. We used an expanded subset of DEGs (DESeq2, $p < 0.05$), with 2012 DEGs in Q140K and 1107 DEGs in UOX-iKO, to capture changes in potentially all segments. The descending thin limb had the most DEGs in both models (766 and 479, respectively), whereas the proximal tubule showed the greatest differences (339 DEGs in Q140K and 112 DEGs in UOX-iKO). Although overlap between DEGs in both models was low, where it did occur, many of the genes were altered in opposite directions, mirroring the differences in tubular urate. To better understand renal transcriptional and physiological responses to alternative tubular urate levels, we focused on collecting Aqp2 and Aqp3duct water channels, necessary for water reabsorption to produce concentrated urine. Aqp2 and Aqp3 were up-regulated in Q140K and down-regulated in UOX-iKO. Following 24 h urine collection, we found that Q140K mice had increased urinary osmolarity and lower urine volume, while UOX-iKO mice had decreased urinary osmolarity and higher urine volume. These findings suggest that tubular urate levels may be directly influencing urine concentrating mechanisms at the transcriptional level, altering the probability of urate precipitation. Understanding pathological effects of HU on kidney function and disease requires knowledge of the underlying cause. Here, we show that UX and OP result in significantly altered transcriptional responses to similar levels of elevated circulating urate, implying that patients with UX or OP types of HU may respond differently to treatments. Thus, trials evaluating a potential causal role for urate in human kidney disease must take this into account.

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