A Novel Approach For Uric Acid Crystal Detection In Human Coronary Plaques Ex-Vivo With Cross-Polarized Micro-OCT

Kensuke Nishimiya,[a,b] Gargi Sharma,[a] Kanwarpal Singh,[a] Hany Osman,[a]
Joseph A. Gardecki,[a] Guillermo J. Tearney[a,c,d]

a. Wellman Center for Photomedicine, Harvard Medical School and Massachusetts General Hospital, Boston, Massachusetts, USA
b. Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan
c. Harvard-MIT Division of Health Sciences and Technology, Cambridge, Massachusetts, USA
d. Department of Pathology, Harvard Medical School and Massachusetts Hospital, Boston, Massachusetts, USA

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Nishimiya_Kensuke, MD, PhD.
Research Fellow, Wellman Center for Photomedicine.
Harvard Medical School and Massachusetts General Hospital.
40 Blossom Street, Boston, MA, USA.
(Tel) +1-617-724-2979
E-mail: kensuke118@cardio.med.tohoku.ac.jp
E-mail: x10guisher118@gmail.com

Abstract

***Background*:** Uric acid crystals (UACs) have been identified as a possible therapeutic target for cardiovascular disease (CVD) due to their potential to exacerbate inflammation through inflammatory cytokine activation. UACs are needle-shaped crystals that alter the light polarization through their birefringent properties. Relatively, little is known about the existence of UACs in human coronary plaques because of a lack of a reliable methodology for imaging these subcellular structures. Here we introduce a new mode of OCT with 1-μm resolution, termed cross-polarized micro-optical coherence tomography (CP-μOCT). In the present study, we examined whether or not CP-μOCT enables identification of UACs in human coronary arteries with a history of gout.

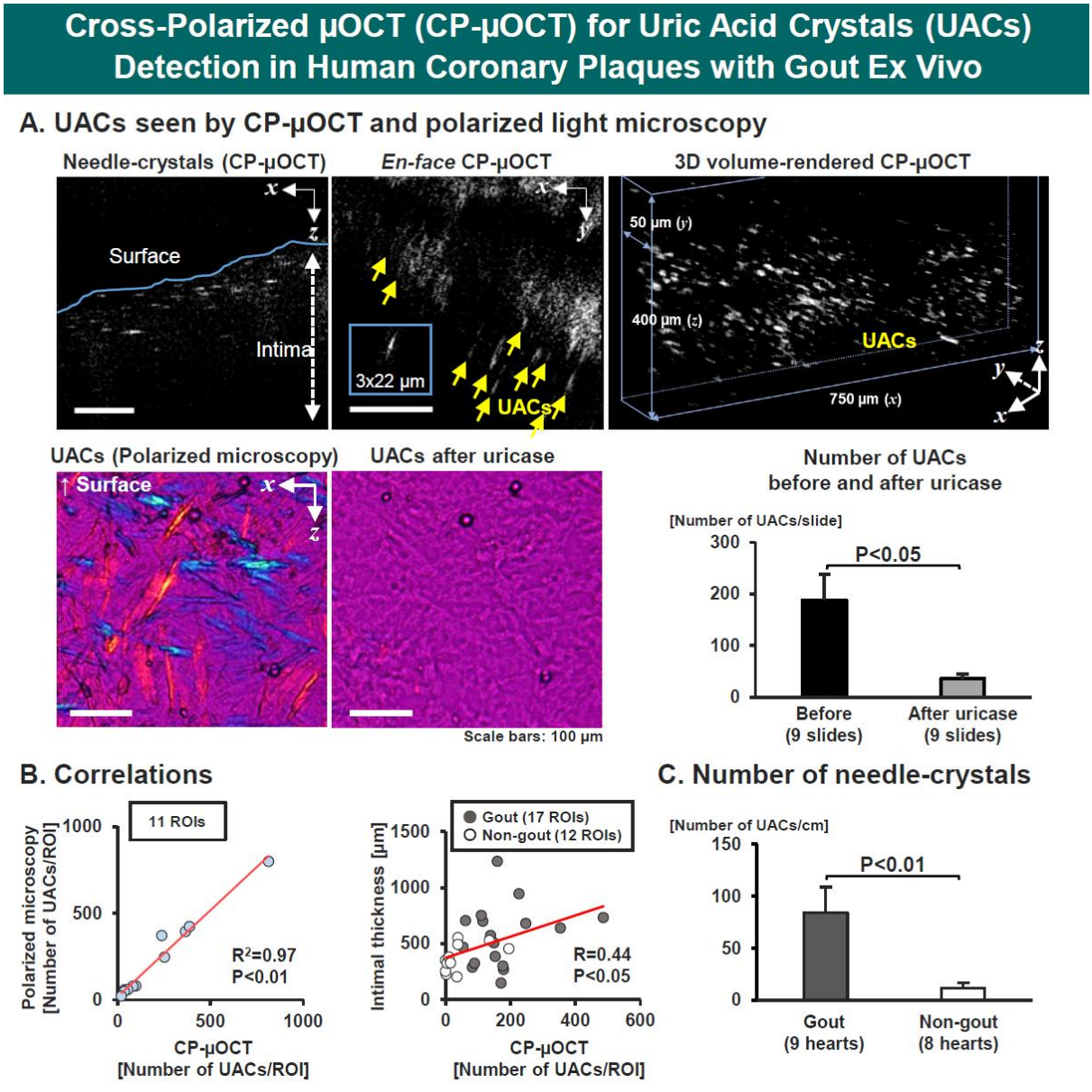
***Methods*:** Human cadaver coronary arteries with a history of CVD with (n=9) or without gout (n=8) were dissected for CP-μOCT imaging. Specimens were processed for identification of birefringence under polarization microscopy. To confirm that the crystals observed by CP-μOCT were UACs, sections were immersed in uricase (an enzyme that oxidizes UA) to confirm dissolution. To count UACs, CP-μOCT was volume-rendered in 3Ds (**Fig. A, upper right panel**). UACs were counted in three-dimensions in regions of interest sized (750 (*x*) x 500 (*y*) x 400 (*z*)). Final crystal counts were normalized by the total coronary length utilized. The relationship between CP-μOCT delineated UAC counts and UACs seen in corresponding histology was analyzed using linear regression and the difference in coronary UACs amongst gout vs non-gout patients was analyzed using t-tests.

***Results*:** CP-μOCT clearly visualized needle-crystals that appeared as long projections in only two orthogonal planes, and polarization microscopy confirmed that CP-μOCT delineated needle-crystals demonstrated negative birefringence (**Fig. A, upper panels**). These crystals were dissolved after immersion in uricase ($P<0.05$) (**Fig. A, middle panels**), and thus were presumably UACs. CP-μOCT-delineated UACs were significantly correlated with UACs counted by polarization microscopy based histology ($R^2=0.97$, $P<0.01$), and with

histology-derived intimal thickening (R=0.44, P<0.05) (**Fig. B**). CP-µOCT-delineated UACs were significantly greater in gout patients compared with non-gout patients (P<0.01) (**Fig. C**).

***Conclusions*:** CP-µOCT is capable of identifying birefringent UACs in coronary plaques, potentially making it a valuable tool for studying this mechanism of coronary lesion progression.

***Figure*:**



Gabriela Sandoval-Plata, MSc

Asymptomatic Monosodium Urate Crystal Deposition Associates With Increased Expression of Pro-Inflammatory Genes

Gabriela Sandoval-Plata, Prof. Kevin Morgan, Dr. Tamar Guetta-Baranes, Dr. Ana Valdes, Prof. Michael Doherty, Dr. Abhishek Abhishek. University of Nottingham

Room A26 Clinical Sciences Building

Nottingham City Hospital. Hucknall Road,

Nottingham. UK. NG5 1PB

Phone: +44 79 55 10 25 73

Email: mbxgs2@nottingham.ac.uk

Secondary email: gsandopla@gmail.com

Asymptomatic Monosodium Urate Crystal Deposition Associates With Increased Expression of Pro-Inflammatory Genes

Gabriela Sandoval-Plata [1,2], Prof. Kevin Morgan[2], Dr. Tamar Guetta-Baranes[2], Dr. Ana Valdes[1,3], Prof. Michael Doherty[1], Dr. Abhishek Abhishek[1,3]

[1]Academic Rheumatology, Nottingham City Hospital, School of Medicine, University of Nottingham.
[2]Human Genomics and Molecular Genetics, School of Life Sciences, University of Nottingham.
[3]Nottingham NIHR BRC, Nottingham, UK

Background: Persistent hyperuricaemia is a prerequisite for gout. However, only 10% of people with hyperuricaemia develop symptomatic gout, whereas 25-35% have asymptomatic monosodium urate (MSU) crystal deposits. Whether these asymptomatic deposits are truly inert, or exert a sub-clinical pro-inflammatory effect is unknown. Since the immune response in gout is mediated primarily by the NRLP3 inflammasome, we hypothesized that the presence of MSU crystals in people with hyperuricaemia but no previous gout flares initiate changes in the expression of inflammasome-associated genes.

Methods: Recruitment involved the screening for serum urate (SU) levels and presence of MSU crystals within joints by ultrasonography. Participants were divided into 3 groups: normal SU; high SU without MSU deposits; and high SU with MSU deposits. Peripheral blood was collected and total RNA extracted. RT-qPCR was used to analyse the expression of 86 inflammasome and TLRs-associated genes using a customised QIAGEN Array. Data were normalised to *RPLP0*, and fold changes were calculated using the $2^{-\Delta\Delta CT}$ method. Differences in relative expression among groups were evaluated using the Kruskal-Wallis H test, followed by a 5% false discovery rate to correct for multiple testing. Four gene-clusters -NLRP3 inflammasome-assembly mechanisms, TLRs, NLRP3 inflammasome-effector mechanisms and inflammasome down-regulators- were analysed using linear regression to assess their variation across the groups under study.

Results: A total of 92 participants were included in this study: 31 in the normouricaemia group (SU=312.9±37.3µmol/L), 44 in the hyperuricaemia only group (SU=429.4±44.7µmol/L), and 17 in the hyperuricaemia with MSU crystal deposits group (SU=428.4±49.1µmol/L). Out of 86 genes, nine showed a significant difference among groups ($P_{adj}<0.05$) and a large fold change (FC>1.5) in at least one of the hyperuricaemia groups, compared to the normouricaemia group (Figure 1). *BIRC2, CXCL1, PANX1, TNFSF14 and XIAP* were significantly over-expressed in the asymptomatic MSU deposits group than in the hyperuricaemia only group. *IL-1β* had the largest fold changes in both high SU only (FC=1.9) and high SU with MSU crystals (FC=3.3) groups. Moreover, from the regression models, the TLRs gene-cluster showed the highest R^2 (0.458), followed by the NLRP3 inflammasome-effector mechanism (R^2=0.371), the inflammasome-assembly mechanisms (R^2=0.244) and inflammasome-negative regulators (R^2=0.233).

Conclusion: The differences in the expression of immune-associated genes observed in this study suggest that initial MSU crystal deposition within joints, although asymptomatic, initiates the activation of pro-inflammatory mechanisms. These results reflect systemic responses on gene-expression exclusively, and cytokine assay is underway. Further studies are needed to validate these results in synovial fluid.

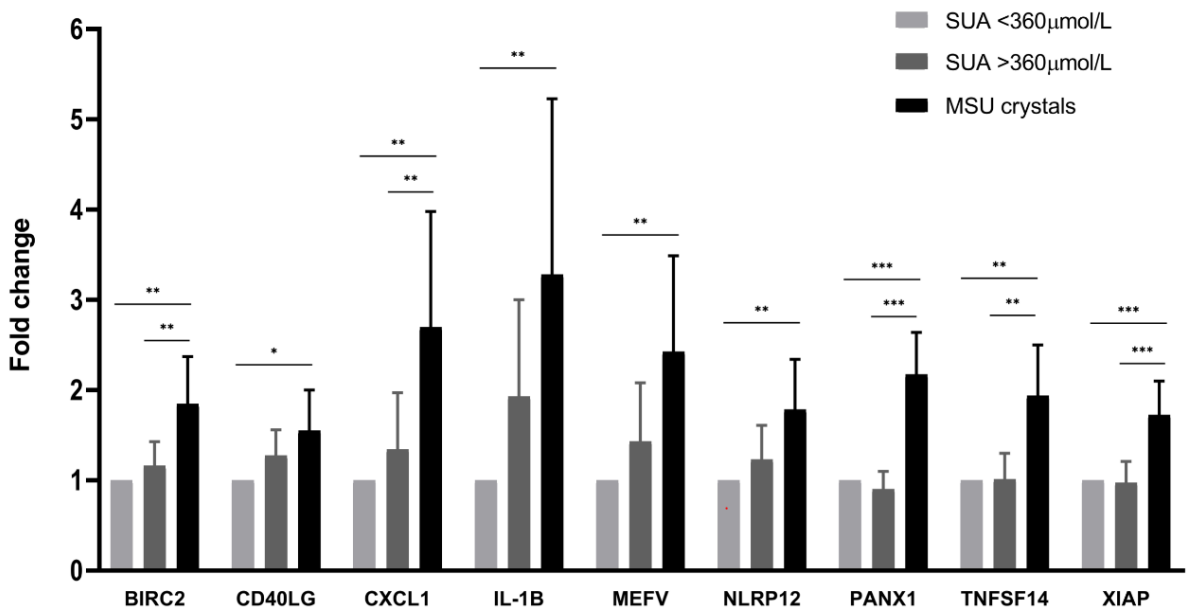


Figure 1. Relative mRNA levels were evaluated by quantitative RT-PCR. The expression was normalised to RPLP0 gene and compared among groups using the Kruskal-Wallis H test. FDR 5% was used to correct for multiple testing. This graph represent significant fold changes relative to the normouricemic group. Note there was not a significant difference between normal SU and high SU without crystal deposits in all genes. *p=0.01, **p=0.001, ***p<0.0001.

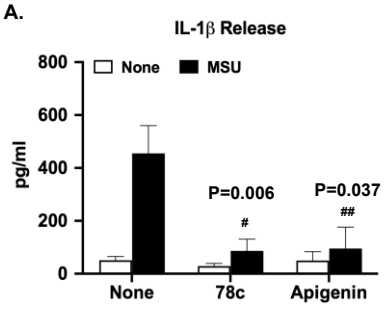
Patricia Gnieslaw de Oliveira, PhD
UCSD Project Scientist
Medicine - Rheumatology, Allergy and Immunology
Gilman Drive 9500 - Stein Research Building Lab. 203 - San Diego-CA
phone - 858 499-9008
e-mail: patty.go@gmail.com
Secundary e-mail: pgoliveira@ucsd.edu

Role of the NAD$^+$ hydrolyzing ecto-enzyme CD38 in regulation of monosodium urate crystal-induced inflammation

Patricia G de Oliveira[1], Paulo VG Alabarse[1], Ygor Marinho[1], Nhi Nuygen[1], Robert Terkeltaub[1,2]and Ru Liu Bryan[1,2]
[1]Division of Rheumatology, Allergy and Immunology, UCSD School of Medicine, 9500 Gilman Drive, La Jolla, CA. [2]VA San Diego Healthcare System, San Diego, CA

Purpose: The leukocyte-expressed type I transmembrane glycoprotein CD38 is a cyclic ADP ribose ecto-enzymatic hydrolase. CD38 functions include degradation of NAD$^+$, and modulation of cell adhesion and calcium signaling. CD38 is an emerging inflammatory marker for monocytes and macrophages, which centrally modulate gouty inflammation. Hence, we examined CD38 for potential regulation of urate crystal-induced inflammatory responses *in vitro* and *in vivo*.
Methods: Mouse bone marrow derived macrophages (BMDMs) were stimulated with urate crystals (0.2 mg/ml) *in vitro*, with use of two CD38 NADase inhibitors apigenin (25 μM), and the highly specific inhibitor 78c (50 μM). We also studied cytokine responses and subcutaneous air pouch inflammation in C57BL/6 mice, using apigenin via gavage (50 μg/day), starting 48 h before urate crystal injection.
Results: Urate crystals significantly increased CD38, NLRP3 and pro-IL-1β gene expression by qRT-PCR analysis. Apigenin and 78c inhibited such effect, and blunted urate crystal-induced production of IL-1β (p=0.006 and p=0.037, respectively) and CXCL1 (p<0.0001 and p<0.0001, respectively) in BMDMs *in vitro* (Figure 1A and 1B). Dietary apigenin reduced numbers of infiltrating leukocytes in response to urate crystals by more than half *in vivo* (p<0.0001, 95% CI of difference: 7.46 to 3.12, Figure 2A). Similarly, urate crystal-induced IL-1β production *in vivo* also was significantly inhibited by apigenin (p=0.029, 95% CI of difference: 1024-273, Figure 2B).
Conclusion: CD38 NADase activity promotes macrophage inflammatory responses to MSU crystals. Pharmacologic inhibition of CD38 NADase activity limits MSU crystal-induced inflammation in experimental gouty inflammation model *in vivo*. Hence, CD38 ecto-NADase activity is a novel therapeutic target for gouty arthritis.

Figure 1 A.



B.

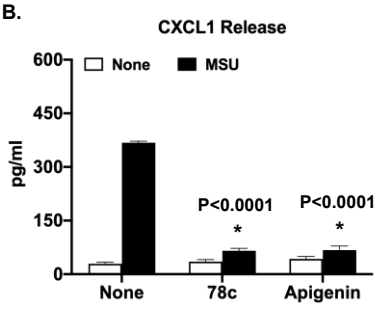
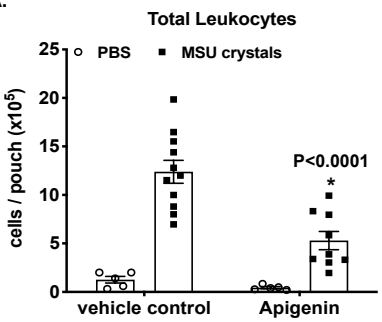


Figure 2 A.



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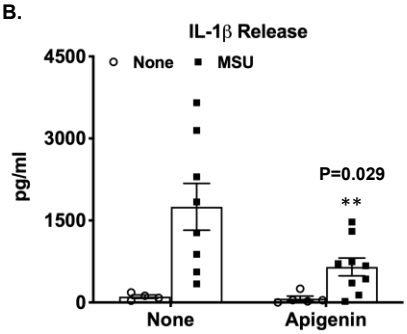


Gabriela Angélica Martínez-Nava, PhD

Tile: Gut dysbiosis in patients with gout and individuals with asymptomatic hyperuricemia

Date submitted: August 1°, 2019

Authors: (1)Gabriela A. Martínez-Nava, PhD; (2)Eder O. Méndez Salazar, MSc; (3)Janitzia Vázquez-Mellado Cervantes, PhD; (1)Yessica Zamudio Cuervas, PhD; (4)Adriana Francisco Balderas, MSc; (1)Karina Martínez Flores Karina, PhD (1)Javier Fernández Torres, (5)Carlos Lozada Pérez, MD; (6)Carlos Pineda Villaseñor, PhD; (7)Austreberto Sánchez González, MD; (8)Luis Silveira Torre, MD; (9)Ana I. Burguete García, PhD; (9)Citlalli Orbe Orihuela, MSc; (9)Alfredo Lagunas Martínez, PhD; (2)Berenice Palacios González, PhD; (1)Alberto López Reyes, PhD

Ascription:

(1) Laboratorio de Líquido Sinovial, Instituto Nacional de Rehabilitación “Luis Guillermo Ibarra Ibarra”
(2) Unidad de Vinculación Científica de la Facultad de Medicina UNAM-INMEGEN, Instituto Nacional de Medicina Genómica
(3) Servicio de Reumatología, Hospital General de México “Dr. Eduardo Liceaga”
(4) Programa de Maestría en Ciencias de la Salud, Escuela superior de medicina, Instituto Politécnico Nacional
(5) Servicio de Reumatología, Instituto Nacional de Rehabilitación “Luis Guillermo Ibarra Ibarra”
(6) División de enfermedades musculo-esqueléticas y reumáticas, Instituto Nacional de Rehabilitación “Luis Guillermo Ibarra Ibarra”
(7) Secretaria de Salud del Estado de Tlaxcala, México
(8) Servicio de Reumatología, Instituto Nacional de Cardiología
(9) Centro de Investigaciones Sobre Enfermedades Infecciosas, Instituto Nacional de Salud Pública

Address: Laboratorio de Líquido Sinovial, Instituto Nacional de Rehabilitación “Luis Guillermo Ibarra Ibarra”. Calz México-Xochimilco 289, Coapa, Arenal Tepepan, 14389 Ciudad de México, CDMX.

Phone: (52)5559991000

Cellphone: (52)7771315257

Email: ameria.justice@gmail.com

Secondary email: gamartinezn@inr.gob.mx

Introduction:
Daily we produce 620mg of urate and to maintain normal levels, most of it is excreted by the kidneys. Nevertheless, approximately 30% of the urate is excreted by the intestine, where trillion of microorganism inhabits. The gut microbiota (GM), the collection of microorganisms that inhabits the intestine, participate in the metabolism of purine and urate. The implication of GM in gout has been described previously in Chinese populations; however, it is still unclear which bacterial genus and which of their genes are responsible for processing and disposal of urate in distinct ethnical background populations, as western populations.

Objective:
To characterize the GM of individuals with gout and asymptomatic hyperuricemia (AH), as well as to identify a bacterial functional profile associated with urate levels.

Methods:
We sequenced the V3-V4 region of the 16SrRNA gene from 135 faecal samples; 59 from patients with gout (ACR-EULAR 2015), 21 from individuals with AH (urate > 7 mg/dL + no history of symptomatic joint or bursa inflammation) and 55 from healthy controls (urate <7 mg/dL without articular symptoms). Those with antibiotic consumption three months prior to the study or with diagnosis of diabetes were excluded. The sequences obtained were processed with QIIME2 and analyzed with LefSe and DeSeq2. Additionally, we predict functional profiles related to each group with Tax4Fun2 software.

Results:
Patients with gout and individuals with AH had a less diverse GM than healthy controls ($p \leq 0.04$ for Chao1, ACE and OTUs observed). Figure 1 depicts the logarithm of the fold change in relative abundance of the genus that were significantly different among the GM of individuals with gout, with AH and healthy controls. The effect size of differentially abundant bacteria genus obtained from LefSe are shown in Table 1. The functional prediction showed that enzymes involved in synthesis of urate are enriched and those related to urate degradation to urea are decreased in the GM of patients with gout with respect to the GM of healthy individuals ($p \leq 1.3 \times 10^{-15}$).

Conclusion:
Our results suggest that gout patients present dysbiosis in their GM, which confers an exacerbated ability to metabolize purines and urate from the diet and a lower ability of their microbiota to transform urate to allantoin a compound 177 times more soluble than urate. The study of GM in patients with AH and gout from diverse ethnic populations and dietary habits could provide new forms of prevention and control of gout.

Figure 1. Bacterial genus that showed a significant fold change in its relative abundance in gout patients (A) and AH individuals (B) with respect to healthy controls.

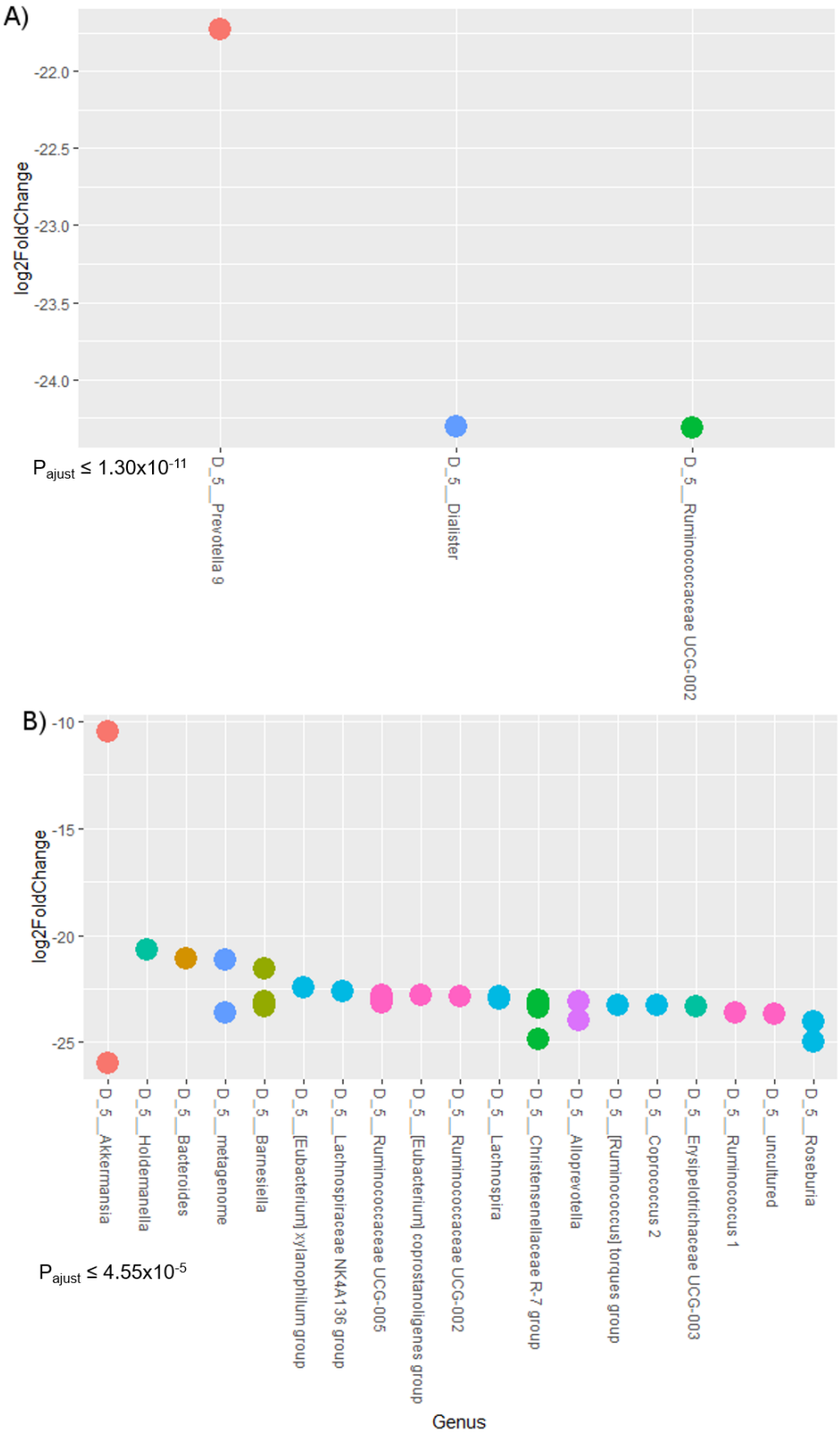


Table 1. Linear discriminant analysis effects of significant bacterial genus by study group.

Bacteria genus	Study group	LDA score	p-value
Ruminococcaceae_DTU089	Control	2.621	0.036
Ruminococcaceae_UCG_014	Control	3.712	0.047
Collinsella	HA	2.896	0.040
Lactobacillus	HA	2.904	0.022
Acidaminococcus	HA	3.129	0.004
Coprococcus_3	HA	3.175	0.044
Akkermansia	Gota	3.872	0.012

LDA: linear discriminant analysis

The Effects of a Low-Fat, Mediterranean, or Low-Carbohydrate Diet on Serum Urate

Date submitted: July 19th, 2019

Chio Yokose, MD; Sharan Rai, MSc; Natalie McCormick, PhD; Na Lu, MPH; Gary Curhan, MD, ScD; Hyon K. Choi, MD, DrPH

Chio Yokose, MD
Division of Rheumatology, Allergy, and Immunology
Massachusetts General Hospital / Harvard Medical School
55 Fruit Street, Bulfinch 165
Boston, MA 02114
Phone: 617-643-4248
Email: cyokose@mgh.harvard.edu
Secondary email: chio.yokose@gmail.com

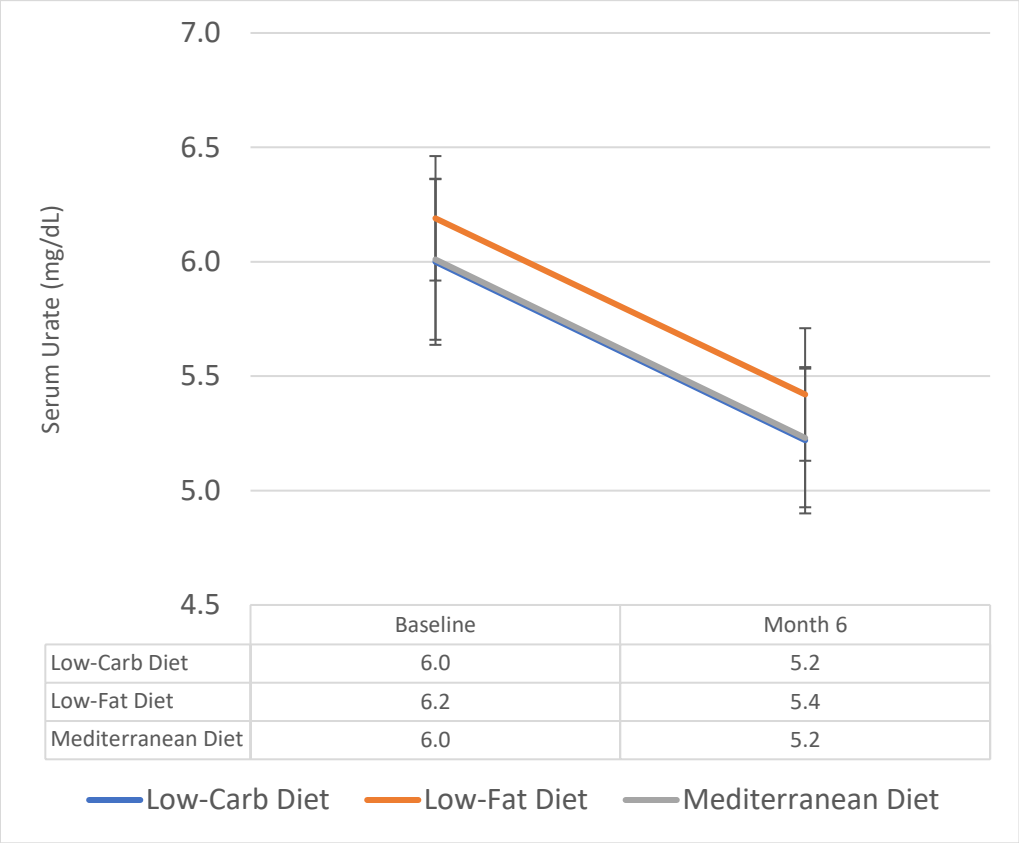
Background: Gout and hyperuricemia are associated with a high burden of cardiometabolic morbidity and mortality. Often, low-purine (i.e., low-protein) diets are recommended for patients with gout. However, such a diet could lead to higher intake of refined carbohydrates and trans-fat, which could worsen the cardiometabolic comorbidities of gout. Conversely, diets that promote weight loss, such as Mediterranean and low-carbohydrate diets, could improve cardiovascular risk factors and may also reduce serum urate (SU) by improving insulin resistance, thereby enhancing urate excretion. However, clinical trial data on the effect of dietary interventions on SU levels are scarce. Thus, we conducted a post-hoc analysis of the Dietary Intervention Randomized Controlled Trial (DIRECT) study to determine the effects of three established weight loss diets on SU levels.

Methods: The DIRECT study included men and women age 40-65 with a body mass index (BMI) of at least 27 kg/m^2 or a diagnosis of either type 2 diabetes or coronary heart disease (regardless of BMI). Participants were randomly assigned to one of three weight loss diets: i. low-fat restricted calorie; ii. Mediterranean restricted calorie; iii. low-carbohydrate non-restricted calorie. We measured SU levels at baseline and 6 months using stored samples from the study from 232 trial participants. The primary outcome of this ancillary analysis was the change in SU from baseline among the three diet groups.

Results: Baseline characteristics were well-balanced between the three groups. All three diets significantly reduced SU levels by 0.8 mg/dL each over 6 months (all p for within-group comparison <0.001 and p>0.98 for between-group comparisons) (**Figure 1**). This urate-lowering effect was most pronounced among those with baseline hyperuricemia (i.e., SU $\geq$ 7mg/dL). The mean SU decrease was 1.9 mg/dL for the low-fat group, 2.0 mg/dL for the Mediterranean group, and 2.5 mg/dL for the low-carbohydrate group. BMI, blood pressure, cholesterol profile, triglycerides, and insulin levels also improved significantly in all three groups (**Figure 2**), with more prominent improvement in the low-carbohydrate group, particularly lipid profiles.

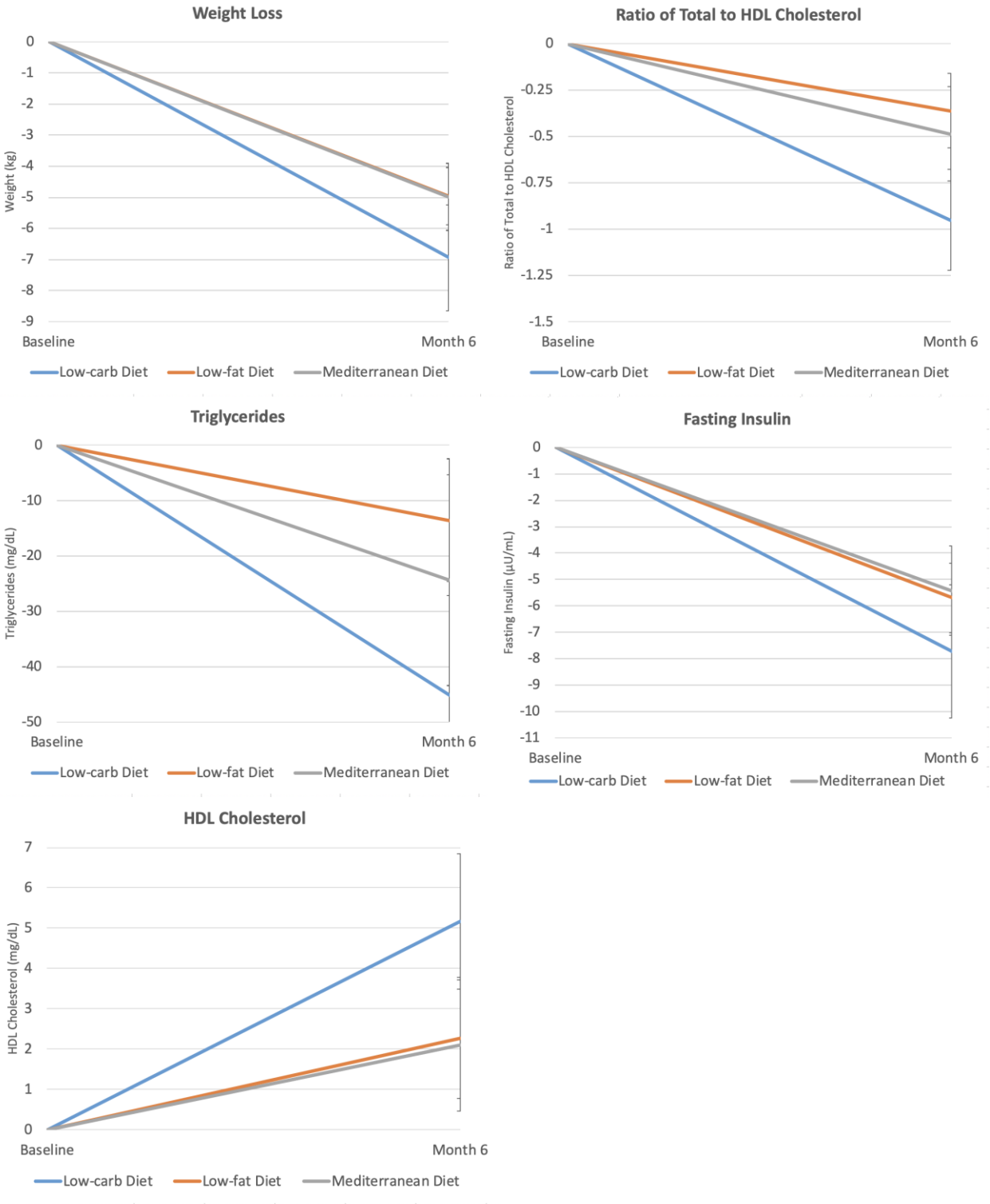
Conclusion: Low-fat restricted calorie, Mediterranean restricted calorie, and low-carbohydrate non-restricted calorie diets can all lower SU levels, although the effect size is smaller than that of a typical urate-lowering drug. Cardiovascular risk factors improved consistently across all three diets. Thus, dietary interventions aimed at weight loss could be a useful adjunctive tool to modestly lower SU levels and improve the cardiovascular risk factors associated with hyperuricemia.

Figure 1: Overall Serum Urate Response According to Diet Group



	Baseline	Month 6
Low-Carb Diet	6.0	5.2
Low-Fat Diet	6.2	5.4
Mediterranean Diet	6.0	5.2

Figure 2: Weight Loss and Cardiovascular Risk Factors Among Those with Baseline Hyperuricemia



Jie Lu, MD, PhD

Tital: Hyperuricemia Predisposes to the Onset of Diabetes via Promoting Pancreatic β-Cell Death in *Uricase* Deficiency Mice

Date: July 24th, 2019

Authors list: Jie Lu, M.D., PhD. (The Affiliated Hospital of Qingdao University, CN);

Yuwei He, PhD. (The Affiliated Hospital of Qingdao University, CN);

Lingling Cui, PhD. (The Affiliated Hospital of Qingdao University, CN);

Changgui Li M.D., PhD. (The Affiliated Hospital of Qingdao University, CN).

Address: Shandong Provincial Key Laboratory of Metabolic Diseases

the Affiliated Hospital of Qingdao University

16 Jiangsu Road, Qingdao 266003, China.

Phone: +86 13127006046

Email: 13127006046@163.com

Secondary email: evausa1988@163.com

(352 words)

Background: Uric acid (UA) is the end product of purine metabolism in humans. Due to the evolutionary disruption of the *Uox* gene encoding urate oxidase (*Uox*) or uricase, humans are vulnerable to hyperuricemia (HU). Uricase expressed in the liver of rodents can further degrade UA into allantoin, which has hindered the establishment of suitable rodent models for HU. Clinical studies have shown a link between HU and diabetes, while the exact effect of soluble serum urate on glucose metabolism remains elusive.

Aims: This study aims to characterize the glucose metabolic phenotypes and investigate the underlying molecular mechanisms using a novel spontaneous HU mouse model which is in absence of *Uox* gene.

Methods and Results: In an attempt to study the role of HU in glycometabolism, we implemented external stimulation on *Uox*-knockout (KO) and wild-type (WT) mice with high-fat diet (HFD) and (/or) multiple-low-dose streptozotocin (MLD-STZ) to provoke the potential role of urate. Notably, while *Uox*-KO mice developed glucose intolerance in basal condition, none had spontaneously developed into diabetes even with aging. HFD-fed *Uox*-KO mice manifested similar insulin sensitivity compared with WT controls. HU augmented the existing glycometabolism abnormality induced by MLD-STZ, and eventually lead to diabetes evidenced by the increased random glucose. Reduced β cell masses and increased the terminal deoxynucleotidyl transferase mediated dUTP nick end labeling (TUNEL) positive β cells suggested HU-mediated diabetes was cell death dependent. Moreover, microarray profiling from isolated islets of STZ-induced *Uox*-KO mice and WT counterparts revealed Pck1 is a possible target gene in HU related β-cell death. Mechanistically, activation of Pparγ-Pck1-mTOR pathway may participant in HU induced β-cell apoptosis. This study suggests that HU accelerates but not causes diabetes by inhibiting islet β-cell survival.

Conclusion: The current study demonstrates that urate *per se* is insufficient to induce diabetes, while impairs glucose tolerance by compromising β-cell function. HU mice is more vulnerable to STZ induced diabetes. For the first time, our research corroborates that high levels of urate predisposes mice to diabetes by disrupting β-cell function using a constitute HU model. Further population based studies are warranted to link the β-cell toxicity of urate and glycol-metabolic disorders.

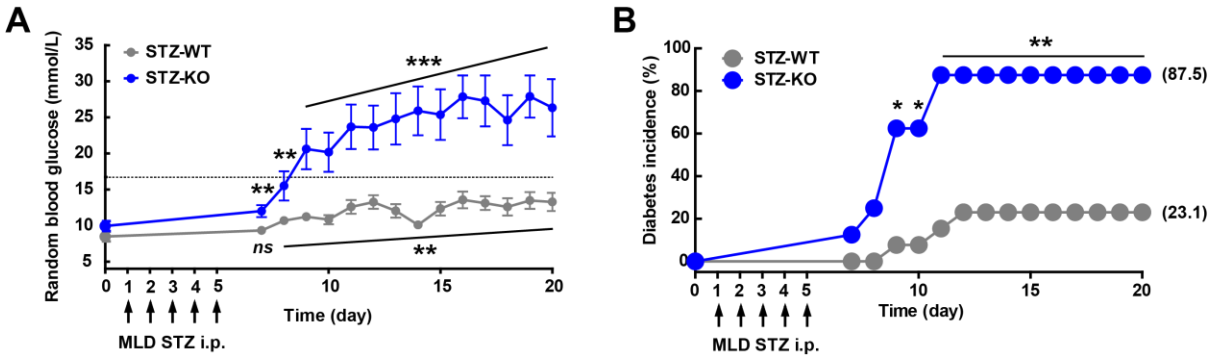
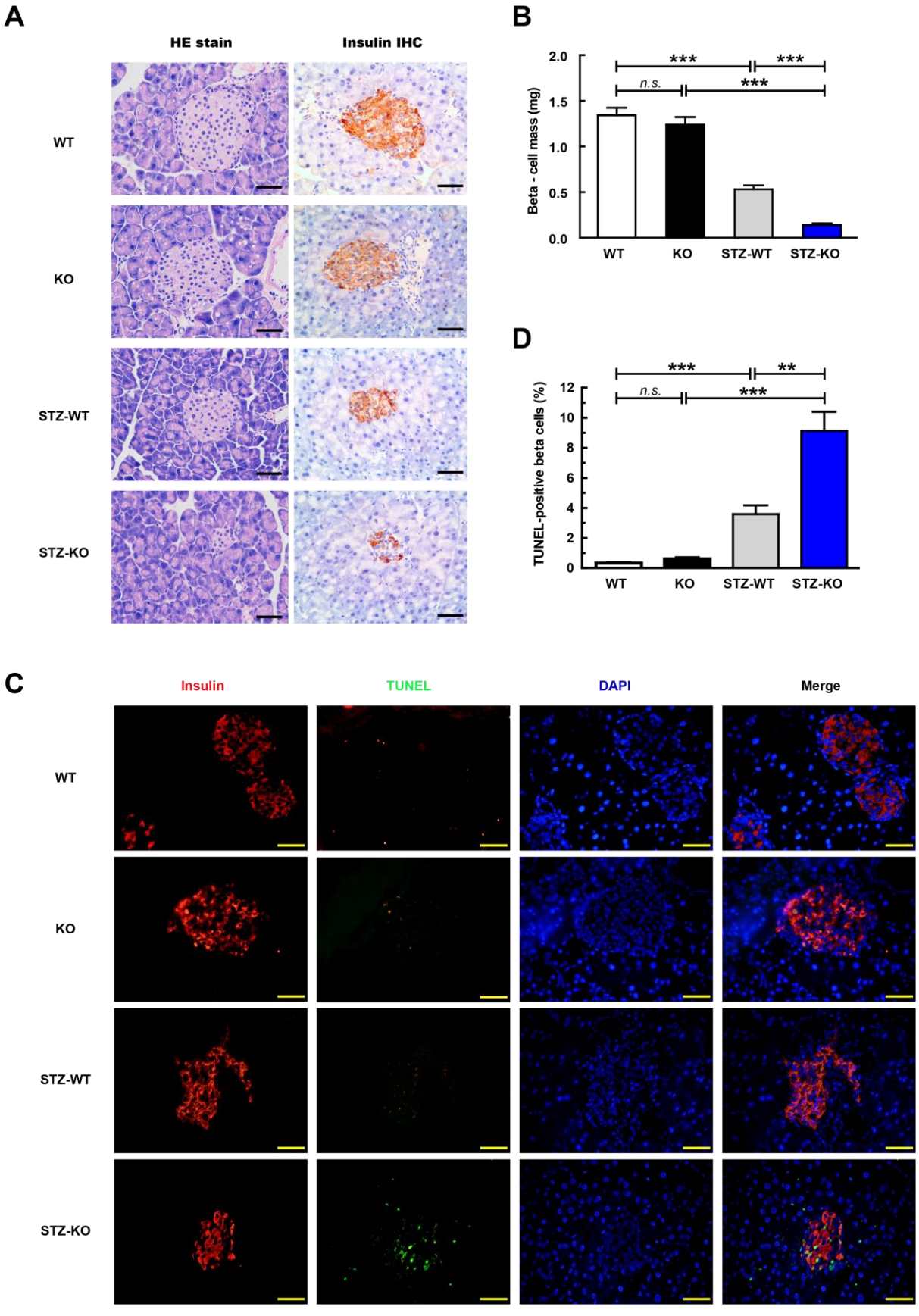


Figure 1. Hyperuricemia induces diabetes with external MLD-STZ stimulation. (*A*) Random blood glucose levels of mice were monitored daily after administration of multiple-low doses streptozotocin (MLD-STZ; 40 mg/kg/d, 5 days) for 20 consecutive days (males, 8-week-old, n = 8, 13 for STZ-induced *Uox*-KO mice and WT mice separately). (*B*) The diabetes incidence of STZ-induced *Uox*-KO mice and WT controls were calculated by percentage (males, 8-week-old, n = 8, 13 for STZ-induced *Uox*-KO mice and WT mice separately). Diabetes was defined as random blood glucose ≥ 16.7 mmol/L. $^{**}P < 0.01$, $^{***}P < 0.001$. Data are expressed as mean ± SEM.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10
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WT
KO
STZ-WT
STZ-KO
C
Insulin
TUNEL
DAPI
Merge
WT
KO
STZ-WT
STZ-KO

Figure 2. Hyperuricemia causes pancreatic β-cell death under MLD-STZ stimuli. (*A*) Pancreatic sections were histologically stained for hematoxylin-eosin (HE) and immunohistochemically stained for insulin, respectively (males, 8-week-old, $n = 6$). (*B*) Total areas of pancreatic tissues and insulin-positive cells were traced manually and determined by counting 10 islets or more in six sections *per* mouse (males, 8-week-old, $n = 6$) in each group. β-cell mass was analyzed and results are shown in multiplying the β-cell ratio (insulin-positive areas/total area) with the initial pancreatic wet weight. (*C*) Insulin-positive cells apoptosis was analyzed by the terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) (males, 8-week-old, $n = 6$). (*D*) Double positive ratio of insulin and TUNEL was measured in each group (males, 8-week-old, $n = 6$). Bars = 20 μm. $^{**}P < 0.01$, $^{***}P < 0.001$, *n.s.*, no significant difference. Data are expressed as mean ± SEM.

Trainee Name: Natalie McCormick, Ph.D.
Department: Clinical Epidemiology Unit, Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital and Harvard Medical School
Mailing Address: 1600-100 Cambridge Street, Boston MA USA 02114
Phone: 617-724-2415
E-mail: nmccormick@mgh.harvard.edu
Secondary e-mail: nmccormick@arthritisresearch.ca

Title: From a Potential Solution to Part of the Problem: Analysis of Public-Payer Spending and Price Trends for Brand-Name and Generic Colchicine and Other Gout Medications

Submission Date: July 21, 2019

Authors: Natalie McCormick, Ph.D.; Zachary S. Wallace, M.D., M.Sc.; Chio Yokose, M.D.; April Jorge, M.D.; Chana Sacks, M.D., M.P.H.; John Hsu, M.D., M.B.A.; Hyon K. Choi M.D. Dr.P.H

ABSTRACT

Background/Purpose:
Little is known about trends and drivers of public spending on gout medications, including colchicine. Used for decades, colchicine's price rose dramatically in the USA after one brand-name formulation (Colcrys) was granted market exclusivity from 2011-2014, as part of the FDA Unapproved Drugs Initiative.

We quantified changes in total spending and unit-prices for gout drugs in Medicare and Medicaid (colchicine, probenecid, allopurinol, febuxostat and pegloticase) and key drivers. We also assessed colchicine prices and spending before, during, and after Colcrys' market exclusivity.

Methods:
We used national Medicare drug spending data for 2012-2017 and Medicaid data for 2008-2017. These contained aggregated prescription claims for >42 million beneficiaries enrolled in Medicare Part B (fee-for-service) or Part D or Medicaid.

We calculated six-year changes in total spending and unit-prices (mean cost/standardized dose) for each drug and in aggregate, in 2017 dollars, and assessed colchicine over 2012-2014 (Colcrys-only period) and 2015-2017 (Colcrys+generics). We performed standard decomposition analyses to isolate four sources of changes in total spending: drug prices, uptake [# recipients], treatment intensity [mean # doses/claim], and annual # claims/recipient.

We included statutory Medicaid rebates (which decrease public spending) and both excluded and included estimated time-varying Medicare rebates (which are paid to insurance plans, not public payers).

Results:
From 2012-2017, annual spending on gout therapies nearly doubled, from $439 to $872 million (**Table**). Colchicine accounted for 39% of 2017 spending, followed by febuxostat (35%), allopurinol (19%), pegloticase (6%) and probenecid (1%).

Spending on allopurinol and febuxostat increased ~200% over six years, driven nearly equally by growth in uptake (e.g., increase of > 800,000 allopurinol recipients) and unit-prices (**Figure**). Pegloticase spending rose >600%, mainly from a >5-fold unit-price hike (from $2,610 to $14,705 per 8mg infusion).

Annual Medicare spending on colchicine rose by 25% over 2012-2014 (Colcrys-only period), from $258 to $324 million, but changed little over 2015-2017 (Colcrys+generics). Still, unit-prices for the generics ($5.13/pill in 2017) were only marginally lower than Colcrys' ($6.78/pill), and considerably higher than colchicine before Colcrys' approval (~$0.50/pill) and the probenecid-colchicine combination pill in any year (~$0.70/pill).

Table: Spending and Utilization for Gout Drugs Covered Under Medicare Parts D and B

Drug (Brand Name)	Drug Unit-Price in 2017	Drug Unit-Price in 2017, Rebate-Adjusted[a]	Total Spending in 2017[b]	# of Recipients in 2017	Change from 2012				
					Drug Prices	Drug Prices, Rebate-Adjusted[a]	# of Recipients	Total Spending[a]	Total Spending, Rebate-Adjusted[a]
Colchicine (Brand-Names + Generics)	$5.81	$4.97	$307,882,574	504,548	8%	16%	37%	19%	28%
Febuxostat (Uloric)	$9.83	$6.88	$287,701,021	125,656	59%	39%	69%	213%	174%
Allopurinol (Generic)	$0.25	$0.25	$151,624,825	1,875,461	80%	80%	76%	242%	242%
Allopurinol (Zyloprim)	$2.70	$1.89	$202,733	288	26%	10%	-16%	10%	-4%
Probenecid (Generic)	$0.59	$0.59	$4,840,475	21,064	5%	5%	-14%	-6%	-6%
Probenecid/Colchicine (Generic)	$0.70	$0.70	$2,779,961	16,769	-16%	-16%	6%	-12%	-12%
Pegloticase (Krystexxa), Part B[c]	$1,838/mg	$1,838/mg	$44,967,319	408	463%	463%	46%	606%	606%
TOTAL: Medicare	-	-	$810,444,607	-	81%	74%	-	98%	100%
TOTAL: Medicare and Medicaid	-	-	$871,825,269	-			-	99%	100%

Data pertains to Medicare Part D, unless otherwise indicated

[a]Applying time-varying manufacturers' rebates on brand-name drugs, ranging from 20% (year 2012) to 30% (year 2017); rebates not applied to generics nor drugs dispensed under Part B

[b]Amounts paid by Medicare, beneficiaries (as deductible, coinsurance, or copayment), and third-parties

[c]Amounts paid by Medicare, beneficiaries (as deductible, coinsurance, or copayment), and third-parties (e.g., supplemental Part B insurance plans)

Trends were similar with and without Medicare rebates (**Table/Figure**).

Conclusion:
Recent increases in public-payer spending on gout therapies were driven by the substantial, >5-fold unit-price hikes for pegloticase and single-entity colchicine, and greater uptake of urate-lowering therapies, the latter being potentially positive. The re-entry of generic formulations did little to mitigate the large financial burden colchicine now imposes on taxpayers and patients.

Front Page

First Author: Ken Cai, MBBS, MSc

Title: The relationship between gout and cardiovascular disease outcomes: a health data linkage study of approximately 1 million New Zealanders using population-level cardiovascular risk prediction equations

Submission Date – July 20, 2019

Authors: Ken Cai, Billy Wu, Suneela Mehta, Nicola Dalbeth, Rod Jackson and Katrina Poppe

Address: Building 502-201, School of Medicine, Faculty of Medical and Health Sciences, University of Auckland, Grafton Campus, 85 Park Road, Auckland, New Zealand, 1023

Phone: +64 28 422 5810

Primary Email: k.cai@auckland.ac.nz

Secondary Email: kenycai@gmail.com

The relationship between gout and cardiovascular disease outcomes: a health data linkage study of approximately 1 million New Zealanders using population-level cardiovascular risk prediction equations

Background/Purpose

Some studies have reported that gout is an independent risk factor for cardiovascular events. Furthermore, urate-lowering therapy such as allopurinol may be associated with reduced risk of cardiovascular disease (CVD). Recently, population-level cardiovascular risk prediction equations for health planning have been developed and validated using linked health data in New Zealand (Mehta, Int J Epidemiol. 2018). We examined the association of gout with population-level estimated CVD risk and CVD outcomes using linked national health data.

Methods

National registries of medicines dispensing data, hospitalisation, and death were linked to the Auckland/Northland regional repository of laboratory results to create a regional health contact population as of January 1, 2012. Approximately 66% (n=968,387) of the resulting health contact population, who were aged over 20 years and had no prior CVD prior to 2012, formed the study cohort. A validated national health data definition of gout was used to identify those with gout: discharge diagnosis of gout (ICD-9 274, ICD-10 M10) from a public hospital admission or having been dispensed gout specific medications (Winnard, Rheumatology 2012), with a primary residence in the Auckland/Northland region for the last 3 years. Baseline estimates of 5-year CVD risk (of cardiovascular death, non-fatal myocardial infarction, stroke, or other vascular event) were calculated using published New Zealand population-level CVD risk scores. The cohort was then linked to national hospitalisations and deaths through to December 31, 2016 (i.e. 5 years follow-up).

Results

Of the 968 387 people included in the study, 34 056 (3.5%) had gout. Estimated CVD risk at baseline and rates of CVD events (fatal and non-fatal) during 5 years of follow-up were higher in both women and men with gout (**Table**). After adjustment for age, gender, ethnicity, deprivation quintile and estimated CVD risk at baseline, gout was independently associated with CVD event rates over 5 years (adjusted HR=1.40, 95% CI: 1.29-1.51 for fatal CVD events and HR=1.31, 95% CI: 1.26-1.37 for non-fatal CVD events). Compared with people without gout, there was no statistically significant difference in adjusted hazard ratio for CVD among those with gout dispensed allopurinol compared with those not dispensed allopurinol (for fatal CVD events, adjusted HR=1.41, 95% CI: 1.30-1.54 vs. 1.33, 95% CI: 1.14-1.55; for non-fatal CVD events, adjusted HR=1.29, 95% CI: 1.24-1.36 vs. 1.37, 95% CI: 1.27-

1.49). There was also no statistically significant difference in adjusted hazard ratio for those with serum urate above 6mg/dL or below 6mg/dL (for fatal CVD events, adjusted HR=1.31, 95% CI: 1.13-1.54 vs. 1.42, 95% CI: 1.27-1.59; for non-fatal CVD events, adjusted HR=1.22, 95% CI: 1.12-1.33 vs. 1.39, 95% CI: 1.32-1.47), when compared to people without gout.

Conclusion

Gout is associated with an increased estimated risk of CVD events calculated from population-level cardiovascular risk equations. Even after adjustment for estimated 5 year CVD risk and additional weighting of risk factors within it, gout independently increased the hazard ratio for fatal and non-fatal events. This effect was not ameliorated by allopurinol use or serum urate lowering to treatment target.

Table. Participant characteristics (*n* = 968 387). Data are shown n (%), except age in years.

	Gout		**Non-Gout**	
	Women	**Men**	**Women**	**Men**
Participants	7147 (20.0)	26909 (79.0)	527402 (56.4)	406929 (43.6)
Median age (IQR)	64 (53-73)	56 (46-66)	44 (32-56)	44 (32-56)
Allopurinol dispensing in people with gout [a]	5110 (71.5)	21280 (79.1)	-	-
Serum urate level monitoring in people with gout[b]	4928 (69.0)	18842 (70.0)	-	-
Population-level CVD risk score				
< 5%	2596 (36.3)	10744 (39.9)	451526 (85.7)	299848 (74.1)
5-10%	2192 (30.7)	6429 (23.9)	47006 (6.5)	54475 (13.5)
10-15%	1364 (19.1)	4803 (17.8)	16131 (3.1)	26580 (6.6)
15-20%	562 (7.9)	2568 (9.5)	5748 (1.1)	11958 (3.0)
> 20%	433 (6.1)	2365 (8.8)	6322 (1.2)	11652 (2.9)
Outcomes				
Fatal CVD events	273 (3.8)	549 (2.0)	2981 (0.6)	2607 (0.6)
Non-fatal CVD events	719 (10.1)	2052 (7.6)	11007 (2.1)	12324 (3.0)

IQR: interquartile range, [a] dispensed at least once in the 5 years prior to January 1, 2012, [b] tested at least once in the last 3 years prior January 1, 2012

Ravi K. Narang, MD

Do Serum Urate-Associated Genetic Variants Influence Gout Risk in People on Diuretics? Analysis of the UK Biobank; July 15, 2019

Narang RK, Gamble G, Phipps-Green AJ, Topless R, Cadzow M, Stamp LK, Merriman TR, Dalbeth N

Department of Medicine, Faculty of Medical and Health Sciences, University of Auckland, 85 Park Road, Grafton, Auckland 1023, New Zealand

Phone: +6499234139
Primary e-mail: r.narang@auckland.ac.nz
Secondary e-mail: narang.rk3@doctors.org.uk

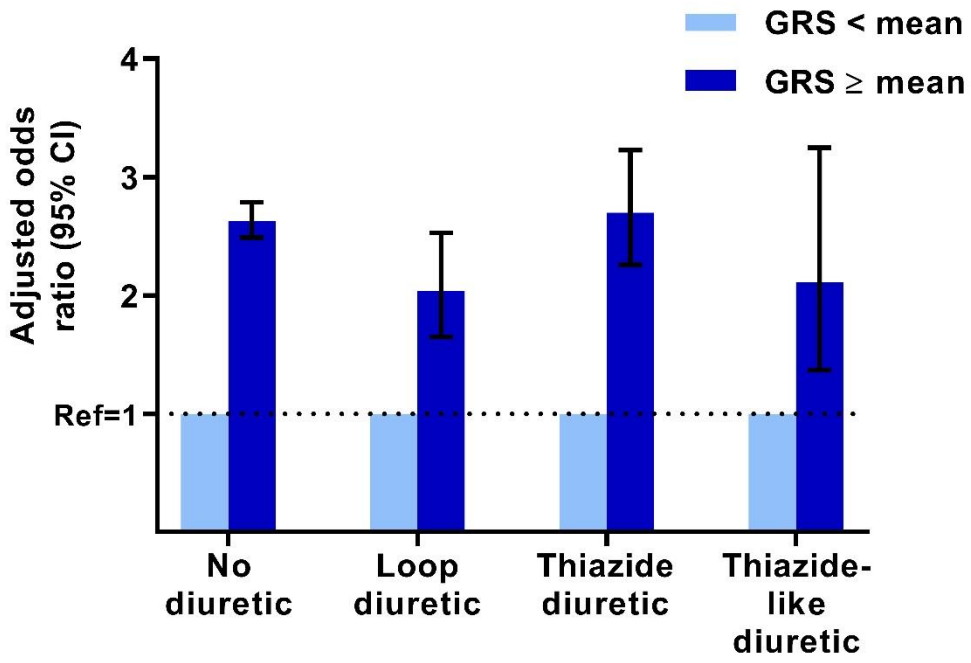
Background: Genome-wide association studies have identified single nucleotide polymorphisms (SNPs) associated with serum urate and gout. An association between diuretic use and gout has also been reported. The aim of this study was to examine whether serum urate-associated genetic variants differ in their influence on gout risk in people taking a diuretic compared to those not taking a diuretic, and to test for interactions between these genetic variants and diuretic use for gout association.

Methods: This research was conducted using the UK Biobank Resource. Participants of European ethnicity, aged 40-69 years, and with genome-wide genotypes were included. Gout was defined using a validated definition (self-report of gout or urate-lowering therapy use). Medication use (including diuretics) and co-morbidity data were collected via self-report. The 10 serum urate-associated SNPs with the strongest association for gout as reported by Cadzow et al (Arthritis Res Ther 2017) were tested for their association with gout according to diuretic use. Gene-diuretic interactions for gout association were tested using a genetic risk score (GRS) and individual SNPs by logistic regression adjusting for age, sex, body mass index, kidney failure, heart failure and hypertension.

Results: Data were available for 359,876 participants, including 7,342 gout cases (2.0%). Gout was present in 1,197 (4.0%) diuretic users and 6,145 (1.9%) non-diuretic users; OR [95% CI] 2.21 [2.08-2.36] for diuretic users compared to non-diuretic users. Compared with a lower GRS (below the mean), a higher GRS (mean or higher) was positively associated with gout in those not on diuretics (OR 2.63 [2.49-2.79]), in those on loop diuretics (OR 2.04 [1.65-2.53]), in those on thiazide diuretics (OR 2.70 [2.26-3.23]), and in those on thiazide-like diuretics (OR 2.11 [1.37-3.25]) with similar ORs and overlapping confidence intervals (Figure). The use of a loop diuretic with the presence of a higher GRS exerted the highest ORs for gout association; compared to non-diuretic users with a lower GRS, the OR for gout was 6.04 [5.18-7.04] in loop diuretic users with a higher GRS.

Conclusion: In people on diuretics, serum urate-associated genetic variants contribute strongly to gout risk, with a similar effect to that observed in those not taking a diuretic. These findings suggest that the contribution of genetic variants is not restricted to people with 'primary' gout and genetic variants play an important role in gout susceptibility in the presence of other risk factors.

Figure: Association between genetic risk score (GRS) and gout according to diuretic use. Data were adjusted by age, sex, body mass index, hypertension, renal failure and heart failure.



Nick Sumpter

Association of a Gout Polygenic Risk Score with Disease Severity Phenotypes Amongst Caucasian Gout Patients in Three Independent Cohorts. July 26, 2019

Nick Sumpter; Alexa Lupi; Ana Vazquez; Richard Reynolds; Abhishek Abhishek; Mariano Andres; Michael Doherty; Lennart Jacobsson; Matthijs Janssen; Tim Jansen; Leo Joosten; Meliha Kapetanovic; Frederic Liote; Hirotaka Matsuo; Geraldine McCarthy; Fernando Perez-Ruiz; Philip Riches; Pascal Richette; Ed Roddy; Blanka Stiburkova; Alex So; Anne-Kathrin Tausche; Rosa J. Torres; Tillman Uhlig; Nicola Dalbeth; Lisa Stamp; Tony R Merriman

Department of Biochemistry, University of Otago

710 Cumberland St

North Dunedin, Dunedin 9016, New Zealand

Trainee mailing address:

Apartment 122, 951 18th St S

Birmingham, Alabama, USA 35255

Phone: (+1) 205-761-8002

Email: nick.sumpter@postgrad.otago.ac.nz

Secondary email: nicholassumpter@uabmc.edu

Aims

This study aimed to determine whether a polygenic risk score (PRS) based on gout-associated genetic variants is associated with gout severity phenotypes including age at onset, presence of tophi and flare frequency.

Methods

A genome wide association study (GWAS) for gout was performed on all genotyped SNPs (single nucleotide polymorphisms) in 409,634 Caucasian individuals (8,192 gout cases) from the UK Biobank cohort. All 129 genome-wide significant SNPs (P < 5e-8) were grouped into 12 loci (+/- 500 kb of top SNP for each locus). The most significant SNP of each locus was selected for analysis in three cohorts of gout patients: the New Zealand Gout Study Caucasian cohort (NZ Gout; 783 males, 161 females), the Ardea cohort (1121 males, 57 females) and the EuroGout cohort (1114 males, 143 females). An odds ratio weighted PRS consisting of the top 12 SNPs was calculated for each individual, then standardized by dividing by the PRS standard deviation (SD) in their respective cohort. The three severity phenotypes were regressed separately against the PRS, with adjustment for age at collection and sex. The regression coefficients were then meta-analysed across the three cohorts.

Results

As expected, the PRS showed a highly significant positive association with gout in the NZ Gout study cohort (OR [95%-CI] = 1.79 [1.60, 2.00], P = 1.46e-23; performed using matched non-gout controls from the NZ population (487 males, 295 females)).

In meta-analysis of all three cohorts, age at gout onset showed a significant decrease of 1.74 [95%-CI: -2.24, -1.23] years for a 1 SD increase in the PRS (P = 2.41e-11).

Presence of tophi was also found to be significantly associated with increasing PRS in the three cohorts (OR_{meta} [95%-CI] = 1.10 [1.01, 1.18], P = 0.021). However, when adjusting for disease duration, the strength of the association was reduced (OR [95%-CI] = 1.08 [0.99, 1.17], P = 0.072).

The number of flares in the past year (out of 52 weeks) did not show a significant association with the PRS in any cohort, or under meta-analysis ($Beta_{meta}$ [95%-CI] = 0.042 [-0.191, 0.275], P = 0.72).

Conclusion

This study shows that gout-associated genetic loci play a significant role in determining the age at onset for a gout patient. The PRS likely also contributes to development of tophi, though there is evidence for further genetic control of tophi outside of disease duration. Flare frequency does not appear to be influenced by gout-associated loci.

Subtypes of Gout Based on Comorbidity Patterns Among Black Adults in the US General Population – Cluster Analysis of the National Health and Nutrition Examination Survey 2007-2016

Date submitted: July 19th, 2019

Chio Yokose, MD; Na Lu, MPH; Michael Chen-Xu, MD, MPH; Michael H. Pillinger, MD; Yuqing Zhang, DSc; Hyon K. Choi, MD, DrPH

Chio Yokose, MD
Division of Rheumatology, Allergy, and Immunology
Massachusetts General Hospital / Harvard Medical School
55 Fruit Street, Bulfinch 165
Boston, MA 02114
Phone: 617-643-4248
Email: cyokose@mgh.harvard.edu
Secondary email: chio.yokose@gmail.com

Background: Gout is associated with many metabolic and cardiorenal comorbidities. Studies have investigated the comorbidity subtypes of gout by cluster analyses; however, such analyses have not yet been performed among Blacks nor confirmed in a general population cohort. Thus, our objective was to identify gout subtypes based on comorbidities using cluster analysis among Black adults with gout in the US general population and to compare these findings to that of White adults with gout.

Methods: We used data from 371 Black and 656 White participants in the 2007-2016 cycle of the National Health and Nutrition Examination Survey (NHANES), a nationally representative sample of US adults with detailed clinical and physical examination data. Diagnosis of gout was based on survey of physician- or health professional-diagnosed gout. We employed Ward's minimum variance clustering method to group patients with gout into clusters (i.e., subtypes) based on comorbidity patterns according to 8 variables: obesity, hypertension, diabetes, dyslipidemia, coronary heart disease (CHD), heart failure (HF), chronic kidney disease (CKD), and non-alcoholic fatty liver disease (NAFLD).

Results: Comorbidities were prevalent among Black and White participants with gout. Cluster analysis identified 5 comorbidity subgroups among Black patients with gout (**Table 1**). All patients in Group 1 had dyslipidemia and hypertension. Group 2 had the highest proportion of patients with diabetes (95%). Group 3 consisted of patients with gout but few other comorbidities. All patients in Group 4 had CKD. Group 5 had the highest proportion of patients with CHD and HF. Cluster analysis among US Whites also identified subgroups with isolated gout and dyslipidemia and hypertension (**Table 2**). It also identified a subgroup that was characterized by heart disease with relatively high rates of CKD. Key differences among Whites was the presence of obese and hypertension only clusters, and the lack of a diabetes group. The

higher prevalence of obesity in Blacks and the smaller number of Black participants likely contributed to these differences.

Conclusion: These findings from a nationally representative sample of Black US adults identified 5 comorbidity subgroups of gout: dyslipidemia/HTN, diabetes, isolated gout, CKD, and heart disease. Notable differences from the French (Richette et al., *Ann Rheum Dis,* 2013) and US White cohorts included the separation of CKD and heart disease and the absence of a group defined by obesity among US Blacks. These subgroups may shed light on differences/personalization of gout risk factors, prognosis, and optimal therapeutic approaches for gout and its comorbidities.

Table 1: Subgroups of Black Patients with Gout Based on Comorbidities

Characteristics	Group 1 (n = 66)	Group 2 (n = 96)	Group 3 (n = 103)	Group 4 (n = 41)	Group 5 (n = 65)
Demographics					
Age, years (SD)	62 (12)	64 (11)	60 (14)	68 (9)	66 (11)
Male gender, n (%)	44 (67)	55 (57)	64 (62)	41 (100)	38 (59)
Body Mass Index, kg/m^2 (SD)	32 (7)	35 (10)	32 (7)	30 (6)	37 (10)
Increased Abdominal Circumference, n (%)	53 (80)	79 (82)	74 (72)	31 (76)	43 (66)
Comorbidities, n (%)					
Obesity	32 (49)	65 (68)	53 (52)	18 (44)	45 (69)
Hypertension	**66 (100)**	94 (98)	65 (63)	41 (100)	64 (99)
Diabetes	0 (0)	**91 (95)**	35 (34)	26 (63)	43 (66)
Dyslipidemia	**66 (100)**	90 (94)	19 (19)	29 (71)	47 (72)
Hypercholesterolemia	**62 (94)**	88 (92)	19 (19)	28 (68)	45 (69)
Hypertriglyceridemia	**10 (15)**	11 (12)	2 (2)	3 (7)	5 (8)
Non-Alcoholic Fatty Liver Disease	0 (0)	12 (13)	1 (1)	0 (0)	1 (2)
Coronary Heart Disease	0 (0)	0 (0)	1 (1)	1 (2)	**36 (55)**
Heart Failure	0 (0)	12 (13)	1 (1)	8 (20)	**50 (77)**
Stroke	8 (12)	10 (10)	11 (11)	7 (17)	10 (15)
Chronic Kidney Disease	0 (0)	0 (0)	0 (0)	**41 (100)**	8 (12)
Malignancy	11 (17)	19 (20)	11 (11)	9 (22)	11 (17)

Table 2: Summary of Gout Subtypes Among French, US White, and US Black Patients with Gout

Gout Patients	Group 1	Group 2	Group 3	Group 4	Group 5
French*	Dyslipidemia	Isolated gout	Obese	Diabetes	CHD, HF, CKD
US Whites	Dyslipidemia, HTN	Isolated gout	Obese	Hypertension	CHD, HF
US Blacks	Dyslipidemia, HTN	Diabetes	Isolated gout	CKD	CHD, HF

*Richette et al., *Ann Rheum Dis,* 2013.

Downregulation of type 1 interferon signaling pathway by uric acid exposure in primary human mononuclear cells

Medeea Badii[1], Tania O. Crișan[1], Viola Klück[2], Boris Novakovic[3], Hendrik Stunnenberg[3], Mihai G. Netea[2] Radu A. Popp[1], Leo A. B. Joosten[1,2] and the HINT Consortium

[1]Department of Medical Genetics, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

[2]Department of Internal Medicine and Radboud Institute for Molecular Life Sciences (RIMLS), Radboud University Medical Center, Nijmegen, The Netherlands

[3]Department of Molecular Biology and Radboud Institute for Molecular Life Sciences (RIMLS), Radboud University Medical Center, Nijmegen, The Netherlands

Introduction

The induction of type 1 interferons (IFN) and interferon-stimulated genes (ISGs) is essential for the host immune response to viral stimuli and can also be induced by other PRR ligands. Interestingly, type I IFNs dampen IL-1 mediated inflammation as IFN-β was shown to inhibit IL-1β production *in vitro* and type I IFN therapy is beneficial in autoimmune and autoinflammatory disorders. A previous report showed transcriptional upregulation of type I IFN pathway genes following urate lowering by rasburicase in whole blood of healthy individuals challenged with uric acid infusion. In this study we assessed whether uric acid treatment inhibits the type 1 IFN signaling pathway in mononuclear cells.

Material and methods

Primary human monocytes were treated for 20h *in vitro* with high concentrations of uric acid solubilized in RPMI (50 mg/dl) or control, followed by stimulation with LPS for another 4h. RNA sequencing was performed in monocytes at 20h and 24h. STAT1 and STAT3 phosphorylation was assessed by flow cytometry in PBMCs and monocytes treated with uric acid 10 or 50 mg/dL. Cytokine response to Poly I:C 50 µg/mL (type I IFN inducer) was assessed in PBMCs cultured for 24 h in the presence or absence of uric acid 50 mg/dl and cytokine production was assessed by ELISA in culture supernatants.

Results

Differentially expressed genes were interrogated using gene enrichment analysis according to GO Biological process and the type 1 IFN signaling pathway was the most significant GO term associated with down-regulated genes. Motif enrichment analysis revealed down-regulation of binding sites for IFN-regulatory factor 1 and 2 and IFN sensitive regulatory element. The stimulation of cells with Poly:IC in presence of uric acid resulted in lower IL-6 cytokine production compared to Poly:IC alone. Uric acid 10 mg/dL or 50 mg/dL resulted in lower levels of phosphorylated STAT1 or STAT3.

Conclusions

Pathway analysis of differentially expressed genes and transcription factor motif enrichment in uric acid treated monocytes showed downregulation of type 1 IFN signaling pathway. This was confirmed by

inhibition of Poly I:C induced cytokine production and diminished STAT1 and STAT3 phosphorylation in presence of uric acid in PBMCs. Further validation studies using IFN-α/β are warranted to describe the modulatory effects of this pathway in response to high uric acid exposure. This could be a potential new mechanism linking soluble urate to inflammatory signaling or to deficient immune responses mediated by type I IFNs.

Sarah Stewart, PhD
Article placement order in rheumatology journals: a content analysis focusing on crystal arthritis articles
June 6, 2019
Sarah Stewart, PhD, Greg Gamble, PhD; Andrew Grey, MD; Nicola Dalbeth, MD.
University of Auckland
85 Park Road, Grafton
Auckland, 1023 New Zealand
Phone: +64 9 923 1747
Email: sarah.stewart@auckland.ac.nz
Secondary email: sj.stewart@outlook.com

Article placement order in rheumatology journals: a content analysis focusing on crystal arthritis articles

Background: The placement order of articles within academic journal issues can influence the prominence of articles. Articles ordered earlier in issues are more likely to be seen, read and cited over time. The aim of this study was to determine whether article placement order bias exists within rheumatology journals for articles about crystal arthritis.

Methods: Original research papers published from 2013 to 2018 in the top general rheumatology journals were reviewed. Data were extracted from each paper, including the rank order within an issue, disease category, downloads and altmetric scores. Within each issue, each article was assigned a standard article placement index (SAPI), defined as the order of the article in the issue/total number of articles (range: 0 to 1). Cumulative density function (CDF) plots with area under the curve (AUC) analyses were used to determine whether the distribution of SAPIs for each disease category were different from the expected distribution if there was no order bias. In addition, odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated to compare the proportion of papers appearing in the first three vs. last three places of an issue. Differences in downloads and altmetrics between the first three vs. last three articles were analysed.

Results: Of the 6,787 articles included, there were 269 (4.0%) crystal arthritis articles, including 260 articles about gout and 9 about calcium crystal diseases. The mean (SD) SAPI for crystal arthritis articles was 0.63 (0.28), and AUC analysis of CDF plots demonstrated a significant deviation of crystal arthritis articles towards the back of issues (P<0.001) (**Figure**). Of the 269 crystal arthritis articles, 29 (10.8%) were in one of the first three places of an issue, compared with 72 (26.8%) in one of the last three places of an issue (OR [95%CI] for first three places 0.33 [0.21, 0.53], P<0.001). Consistent with other disease categories, crystal arthritis articles published in the first three places of an issue had more downloads compared to papers in the last three places (mean rate difference [95% CI] 528 [89, 967]) and higher altmetric scores (mean score difference [95% CI] 5.9 [1.4, 10.4]).

Conclusion: Very few papers about crystal arthritis are published in contemporary rheumatology journals. Furthermore, crystal arthritis articles are more commonly placed towards the back of rheumatology journal issues. Editorial decisions about article placement in rheumatology journals may reflect low prioritization of crystal arthritis, and contribute further to low rates of dissemination about scientific advances in these conditions.

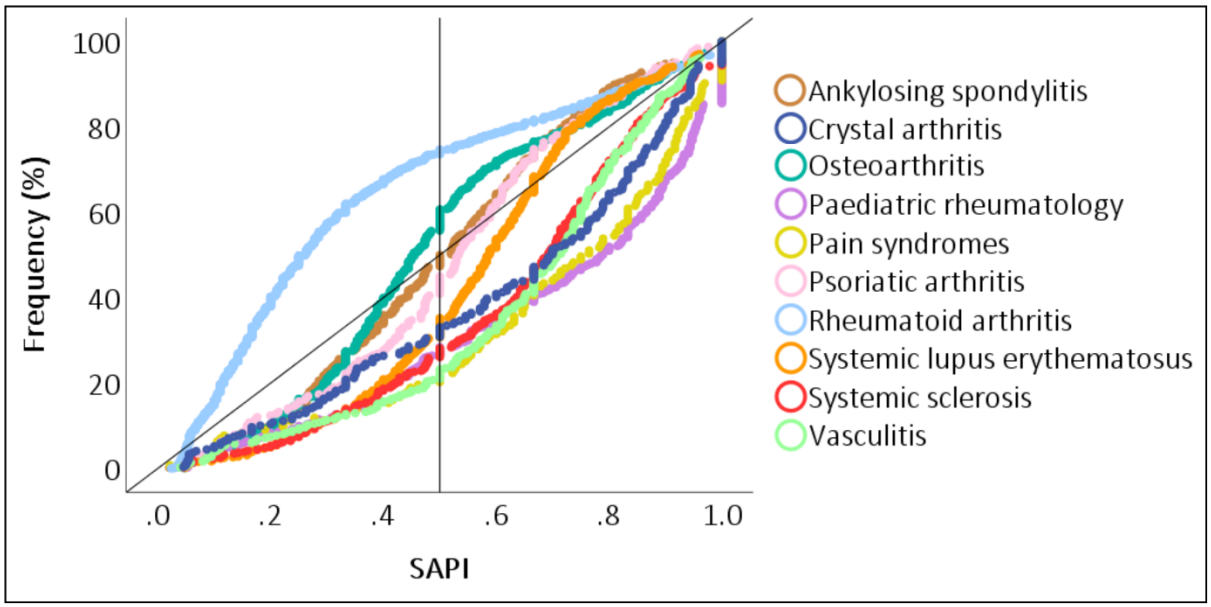


Figure. Cumulative distribution function plots of standard article placement indices (SAPI) for disease categories. Left skewed distributions suggest article placement towards the front of issues.

Sarah Stewart, PhD
How are flares reported in long-term gout clinical trials? A content analysis of randomized controlled trials
June 6, 2019
Sarah Stewart, PhD; Amy Tallon, MBChB; William Taylor, MD; Angelo Gaffo, MD; Nicola Dalbeth MD.
University of Auckland
85 Park Road, Grafton
Auckland, 1023 New Zealand
Phone: +64 9 923 1747
Email: sarah.stewart@auckland.ac.nz
Secondary email: sj.stewart@outlook.com

How are flares reported in long-term gout clinical trials? A content analysis of randomized controlled trials

Background. Prevention of gout flares is a central concern to patients with gout. There are many potential ways that gout flares could be reported in long-term clinical trials. The aim of this study was to analyse methods used to measure and report gout flare outcomes in long-term randomized controlled trials (RCTs).

Methods. A systematic search of electronic databases, supplemented with hand-searching of relevant references lists, was conducted. Articles were included if they were RCTs or articles reporting on analyses of RCT data (i.e. open label extension studies) and reported the impact of an intervention on the prevention of flares in people with gout. The modified Jadad scale was used to assess quality. Gout flare data relating to protocols, outcomes and reporting methods were extracted and synthesised separately for studies of anti-inflammatory prophylaxis and urate lowering/other long term therapy.

Results. A total of 38 articles were included, with 10 reporting outcomes for anti-inflammatory prophylaxis and 28 for urate lowering/other long term therapy. The overall quality score of all articles was good. However, there was marked heterogeneity across trials in gout flare-related entry criteria, flare definitions, data capture methods, reporting methods and time periods used to report gout flares. Anti-inflammatory prophylaxis studies used multiple methods to report gout flare outcomes (mean (SD) 4.3 (2.5) methods/article), while the majority of urate lowering/other long term therapy studies used a single method to report gout flare outcomes. The most common reporting method was the proportion of patients with at least one gout flare (n = 29 articles), followed by the mean number of gout flares per patient (n = 18 articles) (**Table**). Only studies of anti-inflammatory prophylaxis therapy reported flare duration or pain (**Table**).

Conclusion. There is wide variation in methods used to measure and report gout flare outcomes in long-term RCTs. Studies of anti-inflammatory prophylaxis interventions generally report a range of flare characteristics, including incidence, number of flares, flare duration, and pain intensity. In contrast, studies of urate lowering/other long term therapy report limited data, mostly the proportion of participants experiencing flare. These findings support the development of standardized methods to measure and report outcomes that reflect the burden of flares for studies in which gout flare prevention is an outcome of interest.

Table. Number of studies using each gout flare reporting method			
	Method	**Studies of anti-inflammatory prophylaxis therapy (n = 10)**	**Studies of urate lowering/other long term therapy (n = 28)**
Proportion of patients with gout flares	Proportion of patients with ≥ 1 gout flare	7	22
	Proportion of patients with ≥ 2 gout flares	4	1
	Proportion of patients with ≥ 3 gout flares	1	0
	Proportion of patients with ≥ 4 gout flares	0	1
	Proportion of patients with 1 gout flare	2	0
	Proportion of patients with no gout flares	1	0
	Proportion of patients who withdrew from the study due to a gout flare	0	1
	Proportion of patients requiring hospital admission for a flare	0	1
Number of gout flares per patient	Mean number of gout flares	9	9
	Number of gout flares (individual patient data shown	1	0
Number of gout flares per group	Total number of gout flares in each group	3	2
Total number of days in flare per patient	Mean number of gout flare days during follow up	4	0
Gout flare duration per patient	Mean duration of gout flares (days)	2	0
	Median duration of gout flares (days)	1	0
Time to first flare per patient	Median number of days to onset of first flare	4	0

Gout flare pain per patient	Mean pain score due to gout flare in the past week (10 cm VAS)	1	0
	Mean reduction in pain scores during gout flares (10 point Likert scale)	1	0
Total number of days with pain per patient	Mean number of days with a pain severity score $\geq$ 5 (0-10 NRS)	3	0
VAS = visual analogue scale; NRS = numeric rating scale.			

Colchicine Prophylaxis of Gout Flares When Commencing Allopurinol is Very Cost Effective: A health economic analysis

Philip Robinson[1,2], Nicola Dalbeth[3] and Peter Donovan[1,2]

1 Royal Brisbane & Women's Hospital, Brisbane, Australia
2 Faculty of Medicine, University of Queensland, Brisbane, Australia
3 Faculty of Medicine, University of Auckland, Auckland, New Zealand

Background/Purpose: Prophylaxis of acute gout flares when commencing urate lowering therapy is recommended by international guidelines. Whether this is a cost-effective intervention is currently unknown. Colchicine was awarded orphan drug status by the US Food and Drug Administration in 2009 and the price increased from 9 cents per tablet to $5 per tablet (Kesselheim, 2015). Therefore, the economics of using colchicine for all of its indications altered substantially.

Objectives: To perform a cost effectiveness analysis of co-prescribing colchicine when initiating urate lowering therapy for gout using both a United States healthcare system input model and an Australian healthcare system cost input model.

Methods: This cost-effectiveness analysis was completed from the point of view of the third-party payer (This therefore excluded costs such as the cost of the patient driving to their doctor or the hospital). We used a two decision-tree with one arm commencing allopurinol with no colchicine prophylaxis and the other with colchicine prophylaxis. Model inputs were drawn from published literature, where available. We completed univariate and probabilistic sensitivity analysis to confirm the robust nature of the modelling. The time frame for the model was 6 months.

Results: In the US model, the colchicine prophylaxis arm resulted in a cost of US$1109 and 0.49 quality adjusted life-years (QALYs). This was cost-effective compared to placebo (cost of US$536 and 0.47 QALYs, Incremental cost-effectiveness ratio of $25,666 per QALY gained). In the Australian model the colchicine arm dominated placebo (AUD228 in colchicine arm vs. AUD523 in placebo) due to lower colchicine cost. Univariate and probability sensitivity analysis demonstrated that results were robust to changes in input parameters but were most sensitive to cost of colchicine and the rate of reduction of flares from colchicine treatment. In probabilistic sensitivity analysis, the probability of colchicine prophylaxis being the most cost-effective option was 78% in the US and 99% in Australian setting, at a willingness-to-pay threshold of $50,000 per QALY gained.

Conclusion: Colchicine prophylaxis of gout flares whilst commencing allopurinol in gout appears to be cost effective both in the US healthcare system with elevated unit cost for colchicine and in the Australian healthcare system where the unit cost of colchicine is substantially lower.

Adverse events during colchicine use: a systematic review and meta-analysis of randomised controlled trial events

Sarah Stewart, Kevin Yang, Kate Atkins, Nicola Dalbeth, Philip Robinson

Background/Purpose:

Colchicine is a widely used drug used to treat rheumatic and inflammatory conditions. Due to its long historical use in medicine, controlled clinical trials of colchicine have been small, precluding clear understanding about safety profile. The aim of the study was to systematically examine the adverse event (AE) profile of colchicine in randomized controlled trials (RCTs) across all published indications.

Methods: A systematic search was undertaken using electronic databases and manual searching of reference lists. The analysis included double-blind RCTs that compared the effects of oral colchicine to placebo or active comparator. Trials were included if they reported the incidence of AEs per group. AE data were extracted under pre-defined categories: diarrhoea, gastrointestinal events (including diarrhoea), liver events, hematology events, muscle events, sensory events, infection events and death, and any reported AE. Meta-analyses were undertaken to determine the pooled risk ratios (RR) of AEs in the colchicine group compared to the placebo and/or active comparator groups. Subgroup analyses were used to explore the effects of disease indication, dose, and exposure duration.

Results: Thirty-two studies were included involving participants with liver diseases (n = 6), gout (n = 5), Bechet's and related conditions (n = 4), pericarditis and related conditions (n = 6), and other (n = 11). The pooled sample size was 3,774 participants. Any adverse event was reported in 26.6% of colchicine users compared to 20.9% of comparator groups, with an estimated risk ratio (RR) (95% confidence interval (CI)) of 1.72 (1.33-2.23) (**Table**). Sub-group meta-analyses showed no significant difference in RR of AEs in colchicine users between placebo and active comparator groups, or between different disease indications, duration of drug exposure, daily dose or cumulative dose. The RR (95% CI) in colchicine users compared to comparator groups for diarrhoea was 2.63 (1.67-4.16), and for any gastrointestinal AE was 1.97 (1.50-2.58), both $P < 0.001$. The RRs of liver, muscle (including myalgia, cramps, myotoxicity, and weakness), sensory, and infection AEs in colchicine users

compared to comparators were not significant (**Table**). No study reported rhabdomyolysis, hematology AEs or deaths.

Conclusion: Although AEs are more common with colchicine compared with placebo or active comparator, these relate mostly to well-recognized gastrointestinal AEs. Increased incidence of liver, sensory, muscle, infection, or haematology AEs or death was not observed.

Table. Meta-analysis results showing pooled risk ratio of adverse events between colchicine and pooled comparator groups

	N. studies	n/N, % (95% CI) participants		Pooled risk ratio (95% CI)	I^2 (p-value)	Overall effect, Z (p-value)[a]
		Colchicine	Comparator			
Any event	26	437/1641, 26.6% (24.5, 28.8)	370/1773, 20.9% (19.0, 22.8)	1.72 (1.33, 2.23)	86% (<0.001)	4.16 (**<0.001**)
Diarrhoea	17	189/797, 23.7% (20.0, 26.8)	54/712, 7.6% (5.8, 9.7)	2.32 (1.51, 3.57)	39% (0.05)	3.83 (**<0.001**)
Gastrointestinal[b]	27	299/1744, 17.1% (15.4, 19.0)	121/1874, 6.5% (5.4, 7.6)	1.97 (1.50, 2.58)	29% (0.08)	4.88 (**<0.001**)
Liver	12	15/1129, 1.3% (0.8, 2.1)	11/1343, 0.8% (0.4, 1.4)	1.63 (0.76, 3.50)	0% (0.82)	1.24 (0.21)
Muscle[c]	8	33/851, 3.9% (2.7, 5.3)	23/850, 2.7% (1.8, 4.0)	1.41 (0.87, 2.30)	0% (0.90)	1.40 (0.16)
Sensory	2	3/201, 1.5% (0.4, 4.0)	2/190, 1.1% (0.2, 3.4)	1.35 (0.27, 6.74)	0% (0.58)	0.37 (0.71)
Infection	4	42/327, 12.8% (9.5, 16.8)	74/548, 13.5% (10.8, 16.6)	1.19 (0.65, 2.16)	47% (0.13)	0.55 (0.58)

[a]Bolded p-values indicate a significant overall effect in the risk ratio for an adverse event between colchicine and comparator groups. *[b]The gastrointestinal category includes diarrhoea.* *[c]The muscle category includes myalgia, muscle cramps, myotoxicity, muscle weakness and elevated CPK. No study assessed or reported rhabdomyolysis.*

VICKY TAI, MBChB

Do serum urate-associated genetic variants differentially contribute to gout risk according to body mass index? Analysis of the UK Biobank.

Vicky Tai[1], Ravi K. Narang[1], Greg Gamble[1], Lisa K. Stamp[3], Tony R. Merriman[2], Nicola Dalbeth[1]

[1]Department of Medicine, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand

[2]Department of Biochemistry, University of Otago, Dunedin, New Zealand

[3]Department of Medicine, University of Otago, Christchurch, New Zealand

Phone: +64 21 042 2366

Email: vtai282@aucklanduni.ac.nz

Secondary Email: tai.vicky18@gmail.com

Abstract Word Count: 393

Background: Both serum urate-associated genetic variants and body mass index (BMI) are associated with gout risk. The aim of this study was to systematically examine whether serum urate-associated genetic variants differ in their influence on gout risk according to BMI.

Methods: This research was conducted using the UK Biobank Resource. Participants of European ethnicity, aged 40-69 years, and with genome-wide genotypes were included. Gout was defined using a validated definition (self-report of gout or urate-lowering therapy use). Medication use and co-morbidity data were collected via self-report. Participants were divided into three BMI groups (BMI<25 kg/m^2 [low/normal], 25 kg/m^2≤BMI<30 kg/m^2 [overweight], and BMI≥30 kg/m^2 [obese]). The 30 serum urate-associated SNPs reported by Kottgen et al. (Nature Genetics 2013) in the large (>140,000 European participants) Global Urate Genetics Consortium GWAS were tested for their association with gout according to BMI group. A weighted genetic risk score (GRS) for gout risk was calculated to model the cumulative effects for the 30 variants. Gene-BMI interactions for gout association were tested using a genetic risk score (GRS) and individual SNPs by logistic regression, adjusting for age, sex, diuretic use, renal failure, diabetes mellitus, hypertension, hypercholesterolemia, alcohol intake and smoking.

Results: Data were available for 358,728 individuals, including 7,305 gout cases (2.0%). Gout was present in 634 (0.5%) individuals in the low/normal BMI group, 3100 (2.0%) in the overweight BMI group, and 3571 (4.3%) in the obese BMI group. Mean GRS was higher in those with gout compared to those without gout in the low/normal BMI group (mean [SD] 1.82 [0.29] vs 1.65 [0.27], $P=2.45x10^{-60}$), overweight BMI group (mean [SD] 1.83 [0.27] vs 1.65 [0.27], $P<1x10^{-300}$), and obese BMI group (mean [SD] 1.80 [0.27] vs 1.64 [0.27], $P=6.43x10^{-261}$). Compared with a lower GRS (< mean), a higher GRS (≥ mean) was positively associated with gout in all BMI groups. There was a mildly attenuated effect of a higher GRS on gout risk in the obese BMI group compared to the overweight BMI group

($P_{interaction}$=0.046), but no GRS-BMI interaction for comparisons between the low/normal and overweight BMI groups, nor between the low/normal and obese BMI groups. No individual SNP-BMI interactions for gout were observed.

Conclusion: In individuals of European ancestry, the association of genetic factors is mildly attenuated in individuals with obesity compared to overweight. However, even for those with obesity, genetic variants have a strong effect on gout risk.

The role of *IGF1R* in urate induced inflammation

Orsolya Gaal[1], Medeea Badii[1], Dragos Marginean[1], Georgiana Cabau[1], Ioana Hotea[2], Cristina Pamfil[2], Simona Rednic[2], Tania O. Crișan[1], Radu A. Popp[1], Leo A.B. Joosten [1,3], HINT Consortium

[1]Department of Medical Genetics, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[2]Department of Rheumatology, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[3]Department of Internal Medicine and Radboud Institute of Molecular Life Science (RIMLS), Radboud University Medical Center, Nijmegen, The Netherlands

Introduction: Gout is an important inflammatory disease with high prevalence in developed countries. While most research focuses on inflammation due to MSU crystal deposition, a few studies describe that soluble uric acid modulates gouty inflammation. Previous studies identified *IGF1R* as a genetic susceptibility locus for hyperuricemia. Moreover, the IGF1 pathway was recently linked to innate immune memory and proinflammatory events induced by metabolic stimuli. In the present study we hypothesize that the IGF1 pathway could be involved in uric acid induced proinflammatory effects. Moreover, we assess whether *IGF1R* rs6598541 polymorphism may affect the risk of gout development.

Materials and methods: PBMCs from healthy donors were cultured for 24 h with RPMI for control and uric acid or *IGF1* binding protein solubilized in RPMI with 10% serum. After 24h the cells were restimulated with LPS with or without MSU crystals. In parallel, the transcription rate for *IGF1R* was investigated in cells treated with increasing doses of uric acid. The capacity of the cells to be primed with uric acid was evaluated using qPCR and ELISA for IL-1β, IL-6 or IL-1Ra. Moreover, genotypes of gout patients were compared to hyperuricemic (HU) controls of same ancestry. 150 HU controls, 200 gout patients and 200 healthy volunteers originated from Cluj-Napoca, Romania were genotyped by Taqman assay. Data analysis was carried out using the dominant or recessive risk models for the obtained genotypes. Moreover, in another cohort originated from The Netherlands, consisted of 195 gout patients and 306 healthy controls, we replicated the analysis. The association of this SNP to disease status or markers of inflammation has been tested. Cytokine production in response to MSU in the presence or absence of palmitate (C16) or Pam3Cys was assessed and linked to the presence of the SNP.

Results:

The *in vitro* data shows that uric acid does not modulate *IGF1R* gene expression in cells treated with increasing doses of uric acid. Asynergism between uric acid and *IGF1* in the production of IL-1β and IL-6 was observed . Moreover, *IGF1* enhanced IL-1Ra, but the uric acid dependent downregulation of IL-1Ra is not modified. In the given population the *IGF1R* rs6598541 allele and genotype distribution shows a similar pattern between the gout and hyperuricemic subjects. Neither the cohort from Romania nor the one from The Netherlands shows differences in the distribution of the genotypes or alleles. The SNP was not found to be statistically correlated with gout, markers of inflammation, nor cytokine production in the studied groups.

Conclusion: IGF1 does not seem to be involved in uric acid induced proinflammatory responses. Moreover, the IGF1 pathway seems unlikely to modulate uric acid induced inflammation, but further investigations are required. The genetic data showed that the polymorphism in the *IGF1R* gene is not associated to gout susceptibility. In addition, in a functional genetics assay no correlation was found between the SNP and cytokine production. However, further studies in larger cohorts are needed in order to draw more relevant conclusions for the general population.

Key words: *IGF1R,* inflammation, gout, hyperuricemia, SNP

Andrew Shaffer, MD

Longitudinal Variation in Repeat Serum Urate Levels: Relationship with Hyperuricemia Classification

7/19/2019

Andrew Shaffer, MD; Elizabeth J. Rahn; Kenneth Saag, MD; Amy Mudano; Angelo Gaffo, MD; University of Alabama at Birmingham (UAB) Department of Internal Medicine and Division of Clinical Immunology and Rheumatology

4803 Melissa Way
Vestavia, AL 35243

Phone: 703 - 400 - 8757

Email: andrewshaffer@uabmc.edu

Secondary email: shaffer.andrew89@gmail.com

Longitudinal Variation in Repeat Serum Urate Levels: Relationship with Hyperuricemia Classification

Andrew Shaffer, Elizabeth J. Rahn, Kenneth Saag, Amy Mudano, Angelo Gaffo

Background/Purpose: Previous studies have noted significant variation in serum urate (sUA) levels, and it is unknown how this influences the accuracy of hyperuricemia classification based on single data points. Our objective was to determine the accuracy of hyperuricemia classifications based on single data points given the degree of variability observed with serial measurements of sUA.

Methods: Data was analyzed from 85 young adults without gout participating in a single center, double-blinded, crossover trial in which participants were randomly assigned to allopurinol (300 mg daily) or placebo for 4 weeks. Serum urate levels were measured at five clinic encounters (2-4 week intervals between measurements). For this analysis, sUA levels collected without intervention: at screening, pre- and post-placebo and after a washout were used (up to 4 sUA levels per participant). Mean coefficient of variation (CV) for sUA was determined. The rates of conversion from normouricemia (sUA ≤6.8 mg/dL) to hyperuricemia (sUA >6.8 mg/dL), and from hyperuricemia to normouricemia were calculated. The rates of conversion to hyperuricemia were then compared across subgroups defined by sUA mg/dL level at initial screening (4-4.4, 4.5-4.9, 5-5.4, 5.5-5.9, 6-6.8).

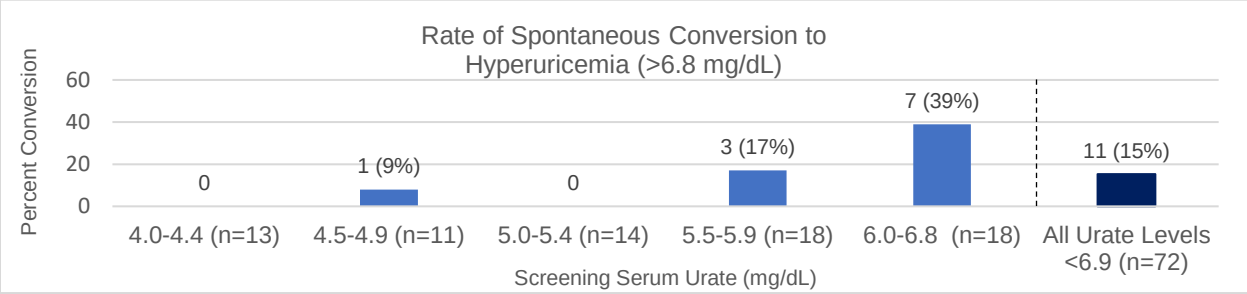
Results: Mean study participant age was 27.8 ± 7.0 years and mean body mass index was 31.1 ± 7.9. 39% of participants were women. 41% of participants were African-American. Mean sUA CV was 8.5% ± 4.9% (1% to 23%). There was no significant difference in the CV between men and women, or between participants with normouricemic or hyperuricemic sUA screening values.

Among those with an initial sUA value in the range of normouricemia (n=72), 15% converted to hyperuricemia during at least one subsequent measurement (figure 1). The subgroup with initial sUA <6.0 (n=54) was much less likely to have future hyperuricemic values compared to the group with screening sUA values between 6.0-6.8 (n=18) (20% vs 39%, p = 0.0037).

Of the study participants with a hyperuricemic screening sUA value (n=13), 46% had normocuricemic values during at least one later measurement.

Conclusion: Single sUA measurements were unreliable in hyperuricemia categorization due to spontaneous variation in urate levels. This is likely a result of multiple factors such as time of sample collection, diet, and weight change. Those with initial sUA values of <6.0 mg/dL were less likely to demonstrate hyperuricemic sUA values at future evaluations, thus a value of <6.0 mg/dL could be a safer threshold to rule out hyperuricemia based on single measurement points.

Figure 1:


Rate of Spontaneous Conversion to Hyperuricemia (>6.8 mg/dL)
Percent Conversion
60
40
20
0
0
1 (9%)
0
3 (17%)
7 (39%)
11 (15%)
4.0-4.4 (n=13)
4.5-4.9 (n=11)
5.0-5.4 (n=14)
5.5-5.9 (n=18)
6.0-6.8 (n=18)
All Urate Levels <6.9 (n=72)
Screening Serum Urate (mg/dL)

Loredana Peca, PhD
Interleukin-1 receptor antagonist 86-bp VNTR gene polymorphism and circulating IL-1Ra concentrations in Romanian patients with gout, July 21, 2019
Loredana Peca, Ioana Hotea, Valentin Nica, Dragoș H. Mărginean, Orsolya Gaal, Cristina Pamfil, Simona Rednic, Tania O. Crișan, Radu Popp, Leonardus A.B. Joosten
Str Pasteur no. 6, Department of Medical Genetics, Iuliu Hațieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
Phone: +40-7744-00353
Email: danapeca@gmail.com
Secondary email: loredana.peca@umfcluj.ro

Title: Interleukin-1 receptor antagonist 86-bp VNTR gene polymorphism and circulating IL-1Ra concentrations in Romanian patients with gout

Authors: Loredana Peca[1], Ioana Hotea[2], Valentin Nica[1], Dragoș H. Mărginean[1], Orsolya Gaal[1], Cristina Pamfil[2], Simona Rednic[1,3], Tania O. Crișan[1,4], Radu Popp[1], Leonardus A.B. Joosten[1,4], The HINT Consortium

[1]Department of Medical Genetics, Iuliu Hațieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

[2]Department of Rheumatology, Iuliu Hațieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

[3]Department of Rheumatology Emergency County Hospital, Cluj-Napoca, Romania

[4]Department of Internal Medicine, Radboud University Medical Centre, Nijmegen, The Netherlands

Background: Interleukin-1 receptor antagonist (IL-1Ra) modulates IL-1 -dependent signaling and its deficit promotes rampant IL-1-induced inflammation. In humans, IL-1Ra is encoded by the *IL1RN* gene in which a VNTR polymorphism was shown to be associated with various diseases and to influence IL-1Ra production. The VNTR is situated in intron 2 and consists of 2 to 6 repetitions of an 86-bp fragment, with the alleles I (4 repetitions) and II (2 repetitions) being the most common. The discovery of reduced amount of secreted IL-1Ra in uric acid-primed PBMCs prompted us to investigate the plasma IL-1Ra levels and the association of *IL1RN* 86-bp VNTR polymorphism to gout in Romanian patients.

Methods: Cohorts consisted of subjects with gout (n = 219), hyperuricemic controls (n = 169), and normouricemic controls (n = 201). Genotyping was performed by PCR and electrophoresis. Circulating IL-1Ra was measured from EDTA plasma samples by ELISA. Data analysis was performed using GraphPad Prism 8.0. Genotype distributions were compared using the Chi-Square Test or Fisher's Exact Test, and Odds-based parameters of association were calculated. Plasma IL-1Ra concentrations across groups were compared using Two-way ANOVA and Sidak's Multiple Comparisons Test.

Results: We assessed the genotype of 589 subjects, of which 485 had genotype I/I (used as the reference group). There were differences in the overall genotype distribution ($p < 0.0001$). A number of 62 patients with genotype I/II or II/II were grouped together as being "short-allele" (*IL1RN*2*) carriers. The odds of being an *IL1RN*2* carrier were higher in controls compared to both the hyperuricemia (OR 5.820, 95% CI [2.38 – 13.37], $p < 0.0001$), or gout groups (OR 1.911, 95% CI [1.05-3.33], $p = 0.03$). The carriers of I/I genotype had very similar IL-1Ra levels when compared to *IL1RN*2* carriers in normouricemic group (a 0.859 pg/dl, 95% CI [-394, 395.6] increase in short-allele carriers IL-1Ra levels). For gout patients, the *IL1RN*2* carriers had a somewhat higher IL-1Ra concentration when compared to the reference genotype (a 470.5 pg/dl, 95% CI [-54.21, 995.3] increase).

Conclusions: Contrary to the study of Lo *et al*, performed in Taiwanese gout patients, our study found an association between the 86 bp VNTR and gout, with *IL1RN*2* carriers being more frequent in normouricemic controls. *IL1RN*2* carriers had somewhat higher IL-1Ra concentrations in the gout group when compared to the reference genotype, in concordance with other studies. Since the available plasma IL-1Ra measurements were limited, the detected differences in IL-1Ra levels are not enough to assess any significant interaction between the genotype and cohort on IL-1Ra concentration (interaction $F(1, 172) = 2.6$, $p = 0.108$), but represent a noteworthy trend that will be studied further.

Study support: HINT Project, co-financed from The European Regional Development Fund through the Competitiveness Operational Programme 2014-2020

Tahzeeb Fatima, PhD
The Association Between Urate and CSF Markers of Alzheimer's Disease in a Population-Based Sample of 70-Year-Olds July 6, 2019
Tahzeeb Fatima[1], Lennart T.H Jacobsson[1], Lena Johansson[2], Mats Dehlin[1], Ingmar Skoog[2]
[1]Department of Rheumatology and Inflammation Research, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [2] Department of Psychiatry and Neurochemistry at Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
Phone: 0046-031-3422491
Email: tahzeeb.fatima@gu.se
Secondary email: tahzeebfatima@gmail.com

Background
The diagnosis of Alzheimer's dementia (AD) is preceded by years of progressive cognitive impairment (CI). Mild CI or predementia in AD is characterized by a certain pattern of cerebrospinal fluid (CSF) biomarkers i.e., a decrease of amyloid-β_{42} ($A\beta_{42}$) and hyperphosphorylation of the tau protein. The worldwide prevalence of dementia ranges between 5 to 7% with higher incidence of predementia reported in men before the age of 70-75 years. Urate has been suggested to exert neuroprotective effects and might therefore alter the risk of dementia by virtue of its antioxidant abilities. A long-term follow-up study has recently indicated a protective role of serum urate (SU) in the development of dementia in Swedish women. However, the relationship between urate and predementia remains elusive. The study was aimed to investigate the association between SU and predementia using the baseline data from a cohort of 70-year-olds in Sweden.

Methods
The baseline sample was derived from the population-based H70 Gothenburg Birth Cohort that includes the data of 70-year-old in Gothenburg, Sweden, born during 1944. Overall, the data for 1,203 individuals was collected between 2014 and 2016. For this study, measurements for SU and three CSF markers, $A\beta_{42}$, total tau and phospho tau, were analyzed from a subset (n=322) of the H70 cohort. Data for individuals with baseline prevalent dementia (n=5) was excluded. The information for *APOE* risk allele (for *rs7412* and *rs42935*) was also included. Linear regression was performed to assess the association between SU and each CSF marker. The data was stratified for gender and the *APOE* (+/-) allele.

Results
Overall, 52% of the participants in the analysis were males. A total of 114 individuals were carrying risk allele for *APOE*, with a higher percentage of males (~60%) being the carriers (Table1). Regression analysis indicated only a trend of positive association between SU and Aβ in male subset (β = 0.48 pg/mL, $p = 0.06$), which persisted when assessed in ApoE+ group (β = 0.86 pg/mL, $p = 0.08$). The positive estimate was also observed in female subset (β = 0.11 pg/mL, $p = 0.67$), albeit not significant. No association for SU was observed for both total tau and phospho tau (Table2).

Conclusion
In seventy-year old males we identify a possible protective effect of urate on predementia, defined as decreased CSF levels of amyloid-β and reflecting amyloid build-up in the brain. This effect seems to be further strengthened in the presence of APOE-ε4.

Table 1: Demographic characteristics of the individuals included in the analysis

	All	Males	Females
Total number, n (%)*	317	165 (52.05)	152 (47.94)
Serum urate (μmol/L)Δ	322.96 ± 76.38	355.84 ± 69.39	286.78 ± 66.94
Amyloid-β (pg/mL)Δ	718.94 ± 224.58	701.81 ± 231.58	737.53 ± 214.85
Total tau (pg/mL)Δ	331.09 ± 134.58	335.41 ± 135.93	326.39 ± 133.39
Phospho tau (pg/mL)Δ	49.36 ± 17.18	49.69 ± 17.30	49.01 ± 17.11
ApoE+	114	69	45
ApoE-	197	95	102

*Six out of 317 individuals (one male and five females) were missing the information for ApoE allele, ΔValues presented as mean ± standard deviation, β; Beta, ApoE+; Individuals carrying ApoE risk allele, ApoE-; Individuals carrying other/normal allele.

Table 2: Association of serum urate with markers of predementia

CSF marker (pg/mL)	All		Males		Females	
	β (95% CI)	***p***	**β (95% CI)**	***p***	**β (95% CI)**	***p***

Amyloid-β						
All	0.136 (-0.19 ; 0.46)	0.41	0.485 (-0.02 ; 0.99)	0.06	0.112 (-0.41 ; 0.63)	0.67
ApoE+	0.441 (-0.13 ; 1.02)	0.13	0.861 (-0.12 ; 1.83)	0.08	0.208 (-0.53 ; 0.95)	0.57
ApoE-	0.020 (-0.33 ; 0.37)	0.91	0.102 (-0.41 ; 0.61)	0.69	0.177 (-0.47 ; 0.82)	0.59
Total tau						
All	-0.004 (-0.20 ; 0.19)	0.96	-0.156 (-0.46 ; 0.14)	0.31	0.075 (-0.24 ; 0.39)	0.64
ApoE+	-0.002 (-0.43 ; 0.42)	0.99	-0.028 (-0.68 ; 0.62)	0.93	-0.012 (-0.68 ; 0.66)	0.96
ApoE-	-0.208 (-0.21 ; 0.17)	0.84	-0.152 (-0.43 ; 0.13)	0.28	0.131 (-0.22 ; 0.47)	0.45
Phospho tau						
All	-0.005 (-0.03 ; 0.02)	0.96	-0.025 (-0.06 ; 0.02)	0.19	0.021 (-0.02 ; 0.06)	0.32
ApoE+	-0.004 (-0.057 ; 0.05)	0.86	-0.015 (-0.09 ; 0.06)	0.71	-0.001 (-0.08 ; 0.07)	0.97
ApoE-	-0.0004 (-0.026 ; 0.02)	0.96	-0.021 (-0.05 ; 0.01)	0.23	0.035 (-0.01 ; 0.08)	0.14

CSF; Cerebrospinal fluid, β (95% CI); Beta estimate (95% confidence interval), *p*; p-value, ApoE+; Individuals carrying ApoE risk allele, ApoE-; Individuals carrying other/normal allele.

Auckland University of Technology
Private Bag 92006, Auckland 1142, NZ
T: +64 9 921 9999
www.aut.ac.nz

Contact information

Mike Frecklington, BHSc (Hons), MPhil

The effects of worn and new footwear on plantar pressure in people with gout July 20, 2019

Mike Frecklington, BHSc (Hons), MPhil, AUT University; Nicola Dalbeth, MBChB, MD, FRACP, University of Auckland; Peter McNair, PhD, AUT University; Alain C. Vandal, PhD, AUT University; Peter Gow, MBChB, Counties-Manukau District Health Board; Keith Rome, BSC (Hons), MSc, PhD, AUT University

AUT University, 90 Akoranga Drive, Auckland, 0627, New Zealand

Phone: +649 921 9999 extension 7832

Email: mike.frecklington@aut.ac.nz

Secondary email: mike.frecklington@gmail.com

Auckland University of Technology
Private Bag 92006, Auckland 1142, NZ
T: +64 9 921 9999
www.aut.ac.nz

The effects of worn and new footwear on plantar pressure in people with gout

Mike Frecklington, Nicola Dalbeth, Peter McNair, Alain C. Vandal, Peter Gow, Keith Rome

Background: In clinical trials, good quality athletic shoes offer short-term improvements (two-months) in foot pain and disability in people with gout, but these improvements are not sustained over time. One reason for this may be wear and subsequent changes to the structural integrity of the shoe. This study tested the effects of wear by comparing the plantar pressures in athletic shoes that had been worn for six months, compared to a new shoe of the same model and size, in people with gout.

Methods: Forty people with gout participated in a cross-sectional repeated measures study. All participants wore a pair of commercially available athletic footwear (ASICS GEL-Cardio Zip 3) for 6 months. Participants completed self-reported footwear diaries to record footwear use over the six months. At the end of the six month period, participants attended a study visit in which the worn footwear was compared with a new pair of the same model and size of footwear. Wear characteristics of the worn and new shoes' upper, midsole and outsole were evaluated. Plantar pressure variables (peak plantar pressure and pressure time integrals) across seven regions of the foot were measured in random order in the two footwear conditions (worn and new). Participants' self-selected speed was monitored during all trials. Wear characteristics of the worn and new shoes were analysed using paired t-tests and Fisher's exact tests. Plantar pressure data were analysed using linear mixed models.

Results: Participants wore their footwear on average of 20 hours per week over the 6 month period. The worn shoes had higher medial midsole hardness ($P<0.0001$), lateral midsole hardness ($P<0.0001$) and heel midsole hardness ($P<0.0001$). Signs of outsole wear was

Auckland University of Technology
Private Bag 92006, Auckland 1142, NZ
T: +64 9 921 9999
www.aut.ac.nz

evident in the worn shoes, with the majority displaying normal upper (P<0.0001), midsole (P=0.005) and outsole (P<0.0001) wear patterns. Comparison of the worn and new shoes showed no significant differences in peak plantar pressures across the seven masked regions. However, lower pressure time integrals were observed at the first metatarsophalangeal joint (P<0.0001), second metatarsophalangeal joint (P<0.0001) and hallux (P=0.003) with the worn shoes compared to the new shoes, consistent with off-loading of these areas. No significant differences were observed in walking speed between the new and worn footwear conditions (P=0.84).

Conclusion: Signs of upper, midsole and outsole wear are evident in footwear following six months of use. Changes in the properties of shoes following prolonged wear may affect foot function in people with gout.

Youssef M. Roman, PharmD, PhD

Title: Prevalence of rs2231142 in *ABCG2* Parallels the Reported Higher Prevalence of Hyperuricemia and Gout in Filipinos than Non-Filipinos

Authors: **Youssef Roman, PharmD, PhD**[1]; Maarit Tiirikainen, PhD[2]; Jonathan Riel, PhD[3]

[1]University of Hawaii, Daniel K. Inouye College of Pharmacy, Hilo, HI, USA

[2]Genomics Shared Resource, Cancer Center, University of Hawaii, Honolulu, HI, USA

[3]John A. Burns School of Medicine, Department of Obstetrics, Gynecology and Women's Health, Honolulu, HI, USA

Department of Pharmacy Practice

Daniel K. Inouye College of Pharmacy, University of Hawaii

677 Ala Moana Blvd., Ste. 1025,

Honolulu, HI 96813

Phone: (808) 528-4001

Fax: (808) 587-2699

Email: roman2@hawaii.edu

Secondary email: youssefcity@yahoo.com

Introduction:

ATP binding cassette G2 (ABCG2) is a major uric acid efflux kidney transporter. Multiple Genome Wide Association and candidate genes studies have identified the missense rs2231142 G>T (Q141K) variant to be associated with increased urate concentration and higher risk for developing gout across multiple populations. The Filipino population is the second largest Asian population in the US and manifest with a higher prevalence of hyperuricemia and gout compared to non-Filipinos and with documented reduced renal urate excretion. The prevalence of rs2231142 G>T in the overall Filipino population is lacking. Given the strong association between rs2231142 G>T and the development of gout, the objectives of this research were 1) to assess the prevalence of rs2231142 G>T in a Filipino cohort 2) to compare the prevalence of rs2231142 G>T in Filipinos to Caucasians.

Methods:

Deidentified DNA samples linked with limited clinical data, provided by the University of Hawaii biospecimens repository, were used. A customized TaqMan genotyping assay panel was run on the QuantStudio™ 12K Flex Real-Time PCR system. The inclusion criteria in the analyses were age ≥ 18 yrs old and self-reporting of being 100% of Filipino. Exclusion criteria were history of cancer or organ transplant. For statistical analyses, Chi-Squared test was used to assess Hardy-Weinberg Equilibrium and genotype/allele frequencies between the Filipino and Caucasian populations using the 1000 Genomes Project.

Results:

All Filipino DNA samples (n= 190) were extracted from cord blood of young pregnant females with mean (SD) age of 30 (6) yrs. Using pre-gravida weight, the mean (SD) BMI was 24.9 (5.8) Kg/M^2. None of the participants included in the analysis had a documented history of gout. The rs2231142 G>T was in Hardy-Weinberg Equilibrium (P-value = 0.76) and with a call rate of 94%. Compared to the genotype frequencies of GG (78%), GT (21%) and TT (1%) in Caucasians, the frequencies of GG (21%), GT (51%) and TT (28%) in Filipinos were different (P-value <0.001). Compared to the risk allele frequency T (12%) in Caucasians, the frequency of T (46%) in Filipinos was greatly different (P-value <0.001).

Conclusions:

This is the first investigation to address the genetic causes of hyperuricemia and gout in Filipinos. The high prevalence of the risk allele T of the rs2231142G>T in *ABCG2* in Filipinos is directionally consistent with higher prevalence of hyperuricemia and gout in Filipinos than non-Filipinos residing in Hawaii. This may partly explain the documented reduced renal urate excretion in Filipinos.

Title: Alpha-1-antitrypsin and IL-1receptor antagonist in relation to serum urate and inflammatory markers in patients; comparison between with gout, asymptomatic hyperuricaemia and healthy controls.

Authors: Ioana Hotea[1′], Tania O. Crisan[2], Cristina Pamfil[1], Medeea Badii[2], Orsolya Gaal[2], Loredana Peca[2], Andreea Mirea[2], Radu Popp[2], Simona Rednic [1′3], Leo AB Joosten[2′4].

1- Department of Rheumatology "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, Romania

2- Department of Medical Genetics "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, Romania

3- Department of Rheumatology Emergency County Hospital Cluj-Napoca, Romania

4- Department of Internal Medicine, Radboud University Medical Centre, Nijmegen, The Netherlands

Introduction:

Gout is an inflammatory form of arthritis with acute episodes highly dependent on neutrophil involvement. A central role for the inflammatory process in gout belongs to IL-β, naturally modulated by IL-1 receptor antagonist (IL-1Ra). Also, previous studies assessed the role of Alpha-1 -antitrypsin (AAT), a serine protease inhibitor, as an inflammatory modulator due to the effects on neutrophil mediated inflammation in gout. In this study we assessed the association between the AAT, IL-1Ra, serum urate levels (SUA) and inflammatory parameters in patients with gout, asymptomatic hyperuricaemia and a control group of healthy subjects.

Materials and methods:

We included 114 patients with gout, with a minimum of 8 points on the ACR/EULAR 2015 classification criteria, 100 asymptomatic hyperuricaemic patients with SUA levels > 7 mg/dl, and 89 normouricaemic controls matched in age. The inflammatory markers, erythrocytes sedimentation rate (ESR), C reactive protein, and SUA levels were determined by routine laboratory test. AAT and IL-1Ra were determined by ELISA in EDTA plasma samples. Statistical analysis was performed using the Spearman correlation test.

Results:

A significant negative correlation was found between circulating AAT and SUA concentration in the control group. This result was not observed in patients with gout or asymptomatic hyperuricaemia, where a tendency for positive correlation between AAT and SUA or ESR was observed. There was also a significant positive correlation between AAT and ESR in patients with gout, consistent with the role of AAT as an acute phase reactant. IL-1Ra positively correlated with CRP levels and SUA, while no correlation between the levels of AAT and the plasma levels of IL-1Ra was observed.

Conclusion:

We were able to validate previous reported findings in which a negative correlation between SUA levels and AAT was observed. This was not confirmed in the gout and hyperuricaemic patients, in line with the

fact that hyperuricaemic patients often present inflammation which positively correlates with AAT. We also validate the positive correlation between inflammatory marker, CRP and plasma levels of IL-1Ra, and show positive correlation between SUA and IL-1Ra. The results obtained in this study reinforce the dual role that AAT could play in inflammation and further studies are needed to assess the effects of uric acid in AAT and IL-1Ra production.

Contact:

Ioana Hotea

Department of Rheumatology "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, Romania

hoteaioana@yahoo.com

hoteaioana07@gmail.com

Address: Scortarilor street nr 15 ap 5 zip code 400186 Cluj napoca Romania

Phone; +40745203737

Ritch te Kampe, PhD 18-07-2019

Sex Differences in the Clinical Profile among Gout Patients: Cross-Sectional Analyses of an Observational Study

Ritch te Kampe[1,2], Matthijs Janssen[3], Caroline van Durme[1], Tim L Jansen[3], Annelies Boonen[1,2]
[1]*Department of Internal Medicine, Maastricht University Medical Center, the Netherlands*
[2]*Care and Public Health Research Institute (CAPHRI), Maastricht University, the Netherlands*
[3]*Department of Rheumatology,VieCuri Medical Center, the Netherlands*

Correspondence to: Ritch te Kampe, Dept. Rheumatology, Maastricht University Medical Center, P.O. Box 5800, 6202 AZ Maastricht, the Netherlands. E-mail: r.tekampe@maastrichtuniversity.nl, secondary e-mail: ritchkampete@hotmail.com, Tel: +31 06 52 11 56 67

Background: Gout is considered a predominantly male disease and current research findings mainly apply to males. To improve insight into sex differences, this study compared clinical and biochemical characteristics between females and males and explored whether differences remained in patients with gout onset ≥ 55 years.

Methods: Baseline data of newly referred gout patients attending two rheumatology outpatient clinics were used. Gout characteristics and comorbidities between sexes were compared. Additionally, the influence of onset of gout after the age of 55 years on sex differences were evaluated in a first subsample, and fractional excretion of uric acid (FEUa) in a second subsample. For comparisons between sexes independent t-tests and $\chi 2$ tests were used. When comorbidities were the outcome, multivariable logistic regressions were computed to adjust the contribution of sex for age, body mass index (BMI), smoking and alcohol consumption.

Results: In the total sample, 954 patients with gout were included, of which were 161/954 (17%) female and 793/954 (83%) male patients. Females were 2.6 years older as compared to males, had a 2.2 kg/m^2 higher BMI with a 2.09 times increased prevalence of obesity, had a 0.04 mmol/L higher sUA-level, used 3.5 times more frequent diuretics, and consumed 0.35 times less likely alcohol. In addition, females had a significantly higher prevalence of comorbidities compared to males, including hypertension (OR: 2.76 (95% CI: 1.86-4.10)), heart failure (OR: 2.30 (95% CI: 1.50-3.53)), DM2 (OR: 3.11 (95% CI: 2.15-4.48)), and had a 14.9 mL/min per 1.73m2 lower eGFR, even after adjustment for age and lifestyle factors (BMI, smoking and alcohol consumption). The sex differences in clinical characteristics and comorbidities attenuated in patients with gout onset ≥ 55 years, yet female still have a higher prevalence of DM2 (OR: 2.05 (95% CI: 1.06-3.97)) and obesity (OR: 2.77 (95% CI: 1.53-5.03)) after adjustments for confounders. Data suggested that underexcretors (FEUa <4.0%) are less frequently encountered in the females (n=11 (36%) vs n=85 (45%)).

Conclusion: This study confirms sex differences in clinical characteristics and comorbidities, but revealed that differences were attenuated in patients with an onset of gout ≥ 55 years. It is indicated that sex-specific differences in clinical characteristics and comorbidities in the currently identified patients can only partly be explained by age and the potentially modifiable lifestyle factors.

Characteristics 374/350-400

Ying Chen , Ph.D, MD

Prevalence and trends of hyperuricemia among residents aged 18 to 40 years old in cosatal areas of Shandong province, China. 2004-2014. July 18, 2019

Ying Chen, Jie Lu, Min Yang, Yangang Wang, Can Wang, Ruixia Sun, Zhongchao Wang, Fang Wang, Changgui Li

Department of Endocrinology & Metabolism, The Affiliated Hospital of Qingdao University

No. 16, Jiangsu Road, Shinan District, Qingdao, Shandong Province, China

Phone: (+86) 18661801696

Email: 18661801696@163.com

Secondary email: 15552657931@163.com

Prevalence and trends of hyperuricemia among residents aged 18 to 40 years old in cosatal areas of Shandong province, China. 2004-2014.

Ying Chen, Jie Lu, Min Yang, Yangang Wang, Can Wang, Ruixia Sun, Zhongchao Wang, Fang Wang, Changgui Li*

Department of Endocrinology and Metabolism, the Affiliated Hospital of Qingdao University, Qingdao, China; Shandong Provincial Key Laboratory of Metabolic Diseases and Qingdao Key Laboratory of Gout, the Affiliated Hospital of Qingdao University, Qingdao, China; Institute of Metabolic Diseases, Qingdao University, Qingdao, China.

Objective To investigate the prevalence and influencing factors of hyperuricemia among residents aged 18 to 40 years old in cosatal areas of Shandong Province, China from 2004 to 2014.

Methods Epidemiological surveys were conducted in 2004, 2009 and 2014 among residents aged 18 to 40 years old living in Yantai, Weihai, Rizhao, Dongying and Qingdao of Shandong province for 5 years or more by random, stratified and cluster sampling. After excluding repeated investigators, a total of 5837 cases met the criteria, including 2124, 2035 and 1978 in 2004, 2009 and 2014, respectively, 2978 males and 3159 females among the cohort. The study population was divided into two groups aged 18 to 30 years and 30 to 40 years.

Result 1**.Age and sex distribution of the prevalence of hyperuricemia**

The prevalence of hyperuricemia in the total population has increased significantly in the past ten years, with 10.7%, 13.8% and 16.9% in 2004, 2009 and 2014, respectively. The prevalence of male population was 17.7%,

21.9% and 26.7%, and that of female population was 4.1%, 6.5% and 7.3%. The prevalence of hyperuricemia in the group aged 18 to 30 years increased significantly since 2004, but that in the group aged 30 to 40 years remained stable. The prevalence of hyperuricemia in the group aged 18 to 30 years was significantly higher than that in the group aged 30 to 40 years of male population in 2014 and of female since 2009. 2.**Risk factors of hyperuricemia** Logistic regression analysis suggested that the risk factors of hyperuricemia were overweight, obesity, abdominal obesity, hypertriglyceridemia, higher frequency of shellfish consumption in male and abdominal obesity, hypertriglyceridemia, higher frequency of fish consumption in female.

Conclusion The prevalence of hyperuricemia have increased significantly among residents aged 18 to 40 years in the coastal areas of Shandong province in 2004-2014, especially among the group aged 18 to 30 years, so the awareness of prevention should be improved and screening should be carried out as soon as possible. For example, appropriate reduction of fish and shellfish seafood intake, body weight and triacylglycerol control may reduce the serum uric acid levels.

The Prevalence, Incidence, and Burden of Gout in the Veterans Health Administration from 2005-2014

Lindsay N. Helget, MD; Bryant R. England, MD; Punyasha Roul, MS; Alison Ruckstuhl, MS; Ted R. Mikuls, MD, MSPH

Character count: 2898

Background/Purpose:

As the largest integrated health care system in the U.S. with a patient population enriched with gout risk factors, the Veterans Health Administration (VHA) represents an ideal data source to evaluate the epidemiology of gout. The goal of this study was to determine the prevalence, incidence, and burden of gout in the VHA from 2005-2014.

Methods:

We queried the Veterans Affairs (VA) Corporate Data Warehouse from 1/1999-12/2014 for inpatient and outpatient encounters, gout diagnoses, and urate lowering therapies (ULT). Gout was classified by the presence of ≥2 outpatient or ≥1 inpatient ICD-9 codes for gout (274.X). In sensitivity analyses we included subjects with ≥1 inpatient or outpatient gout code. We estimated the prevalence and incidence of gout from 2005-2014 using the period from 1999-2004 as a lead in to minimize misclassification of prevalent as incident cases. Prevalence and incidence were further stratified by sex, age (>20-40, >40-60, >60-80, >80 years), and race (white non-Hispanic, black non-Hispanic, white Hispanic, black Hispanic). Gout burden was determined by the proportion of subjects with an ambulatory encounter or hospitalization related to gout. ULT use (allopurinol, febuxostat, probenecid, and pegloticase) was determined annually among those with a gout related encounter.

Results:

From 2005 to 2014, the prevalence of gout in the VA increased from 4.24% to 5.79% while disease incidence ranged from 5.8 to 7.4 cases per 1000 patient-years. In sensitivity analyses using a less stringent case definition, the prevalence of gout increased from 7.56% to 12.84% over the same time period while incidence rates ranged from 7.7 to 9.2 per 1000 patient-years **(Figure 1)**. When stratified by sex, males in 2014 had a substantially higher prevalence than females (6.36% and 0.55%, respectively). In the same year, gout prevalence increased progressively with age, ranging from a low of 0.40% in those 20-39 to 9.53% in those >80. When stratified by race, black non-Hispanics had the highest prevalence (7.01%), while black Hispanics had the lowest (3.91%). Of all patient encounters for the year of 2014, 3.95% were related to diagnosis of gout, an increase from 2005. Gout accounted for 1.27% of all hospitalizations in 2014, demonstrating a stable trend from 2005. In 2014, 53% of gout patients were on ULT (50.8% allopurinol, 1.6% febuxostat, <1% pegloticase, and 1.1% probenecid), demonstrating a similar frequency of use over time from 2005.

Conclusion:

Using data from the largest integrated health system in the U.S., we observed an overall gout prevalence approaching 6% among VA beneficiaries with a frequency that has increased by 29% over a ten-year period. While the prevalence of gout has increased in the VA, the use of ULT has remained stable over the same time frame.

Figure 1. Prevalence and incidence of gout in the Veterans Health Administration from 2005-2014.