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Development of gout in people with asymptomatic hyperuricemia: study protocol for a 5-year prospective cohort

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ABSTRACT

Introduction The central biochemical cause of gout is hyperuricemia (elevated serum urate levels). Ultrasound features of monosodium urate (MSU) crystal deposition are common in people with asymptomatic hyperuricemia. However, it is unclear whether this is a precondition for the development of gout. This study aims to determine whether ultrasound imaging evidence of MSU crystal deposition predicts development of symptomatic gout over 5 years, in people who already have an increased risk of gout due to elevated serum urate concentrations (≥8 mg/dL).

Methods and analysis This is a prospective, international, multicentre study. The study population comprises over 250 participants with asymptomatic hyperuricemia (serum urate ≥8.0 mg/dL). After the baseline assessments, participants are followed for 5 years or until the development of gout, defined by the 2015 American College of Rheumatology/European Alliance of Associations for Rheumatology gout classification criteria. Baseline assessments include anthropomorphic measures, laboratory tests, questionnaires, blood and urine specimen collection, plain radiographs of the feet and standardised ultrasound scans of the lower limbs, scored according to the Outcomes in Rheumatology (OMERACT) gout ultrasound scoring system. The primary outcomes are the development of gout and time course for development of gout in people with and without ultrasound evidence of MSU crystal deposition. Exploratory analyses will examine clinical, genetic and biological factors associated with development of MSU crystal deposition and gout.

Ethics and dissemination This study protocol was approved by the New Zealand Ministry of Health Southern Health and Disability Ethics Committee (MEC/05/10/130/AM16) on 18 December 2018. The findings from this study will be published in peer-reviewed journals and will be presented at national and international conferences.

Trial registration number ACTRN12619000915156.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This multi-centre longitudinal study will investigate the predictive value of ultrasound in the transition from asymptomatic hyperuricemia to gout.
⇒ This study will also analyse other risk factors in the transition to gout, including clinical variables and genetic factors.
⇒ Fluctuations in serum urate between baseline and 5 years will not be captured.

INTRODUCTION

The prevalence of hyperuricemia (elevated serum urate level) is increasing[1] and is a necessary precursor for the development of gout.[2] While the risk of gout increases with higher serum urate levels, previous observational studies have indicated that only half of people with serum urate levels ≥10 mg/dL (0.60 mmol/L) will develop gout over 15 years.[3] Hyperuricemia has also been associated with increased risk of cardiovascular disease,[4] hypertension[5] and kidney disease.[6] However, in most countries, treatment of asymptomatic hyperuricemia in the absence of gout is not recommended due to the unfavourable risk–benefit ratio of urate-lowering therapies.[7]

The last decade has seen considerable advances in the use of imaging techniques, including high-resolution ultrasound, to visualise monosodium urate (MSU) crystal deposition.[8] On ultrasound, MSU crystal deposition can be viewed as double contour signs, aggregates and tophi.[9 10] From cross-sectional studies, it is known that 14%–59% of people with apparently asymptomatic hyperuricemia have ultrasound imaging evidence of MSU crystal deposition.[11–22] These observations suggest that, in the setting of hyperuricemia, MSU crystal deposition constitutes the first stage of the clinical syndrome of gout. These observations have led to a revised model of gout disease progression and staging.[23] This

model proposes a linear progression from asymptomatic hyperuricemia without deposition, to asymptomatic hyperuricemia with deposition, to symptomatic disease.

It is currently unknown when and what proportion of individuals with asymptomatic MSU crystal deposition will progress to symptomatic gout, and the extent to which the increased levels of crystal deposition predict the development of gout; information that is critical to understanding the prognostic implications of asymptomatic MSU crystal deposition in clinical practice as well as assessing the risk–benefit ratio of urate-lowering therapies in those with asymptomatic hyperuricemia. Longitudinal studies are required to establish whether ultrasound imaging findings are necessary preconditions for the development of gout and to determine what pathological mechanisms are responsible for the transition from asymptomatic hyperuricemia to gout. Only a prospective cohort study of persons at risk of gout with careful, regular evaluation can answer these questions.

METHODS AND ANALYSIS

Study design

The Transitions in Gout Research study is a 5-year multisite prospective cohort study. The study has been carried out from June 2019 with enrolment expected to be completed by 31 August 2024. The final study visit is expected to be completed by 31 August 2029. The study is led from Auckland, New Zealand with additional recruiting sites including Wellington and Christchurch (New Zealand), Lille (France), Alicante (Spain), Kaunas (Lithuania), Los Angeles (USA) Qingdao (China) and Mexico City (Mexico).

Objectives

Primary

To determine whether ultrasound imaging evidence of MSU crystal deposition predicts development of symptomatic gout over 5 years in people with hyperuricemia and to describe the time course for development of gout in hyperuricemic individuals with and without MSU deposition on ultrasound.

Secondary

To determine factors associated with developing de novo MSU crystal deposition on ultrasound over 5 years in people with hyperuricemia.

Exploratory

To identify risk factors (including clinical, genetic and biological) for the development of gout in people with hyperuricemia and to determine whether ultrasound evidence of MSU crystal deposition predicts the development of medical comorbidities including cardiovascular disease and kidney disease.

Study population

The target population consists of people with asymptomatic hyperuricemia. Potential participants are identified using point-of-care serum urate metres administered by research assistants within primary and secondary care settings, by public advertising, by advertising through community laboratory reports, and by a mailed invitation to individuals with prior documentation of hyperuricemia measured in the course of usual care, using similar methods to previous research involving participants with asymptomatic hyperuricemia.[24] Screening in primary care is targeted to those with prior documentation of asymptomatic hyperuricemia and those with a higher risk of hyperuricemia (eg, metabolic syndrome, body mass index (BMI) >30 kg/m^2, chronic kidney disease, diuretic use, family history of gout). Individuals with potentially qualifying serum urate levels measured from a point-of-care metre are evaluated with a formal laboratory test to confirm eligible serum urate.

All potential participants are screened to ensure they meet the following inclusion and exclusion criteria. The inclusion criteria are current serum urate of ≥8 mg/dL (0.48 mmol/L); no current or previous clinical symptoms of gout (including flares or clinically apparent tophi); aged between 18 and 80 years and able to provide informed consent according to requirements of local institutional review board (IRB)/ethics committees. The exclusion criteria are: eGFR <30 mL/min/1.73 m² or on renal replacement therapy; serious illness with poor prognosis less than 5 years; other forms of inflammatory arthritis; plans to shift out of area in the next 5 years; previous synovial fluid analysis showing MSU crystals; the presence of subcutaneous tophi; taking urate-lowering therapy (eg, allopurinol, probenecid, benzbromarone, febuxostat), canakinumab or colchicine. Informed consent is obtained from all participants prior to inclusion. Additional consent is obtained for genetic testing of biological samples, but this is not required for participation in the study.

Procedures

The schedule of study visits and assessments is shown in figure 1.

Baseline visit

Eligible participants are evaluated at a baseline study visit, which occurs within 4 weeks of screening. The baseline visit includes recording of demographic information (age, gender, ethnicity, employment status) as well as a physical exam including assessment of BMI (kg/m^2), waist circumference (cm), blood pressure (mm Hg) and the presence of tenderness and swelling using the 66/68 tender and swollen joint counts.[25] An assessment of clinical risk factors is undertaken relating to physical activity habits, dietary habits, alcohol consumption, smoking history and family history of gout. Participants are asked about current medications and present or past comorbidities, including those documented in the modified-Rheumatic Disease Comorbidity Index.[26 27]

At the baseline visit, participants also complete a number of questionnaires to capture health-related quality of life

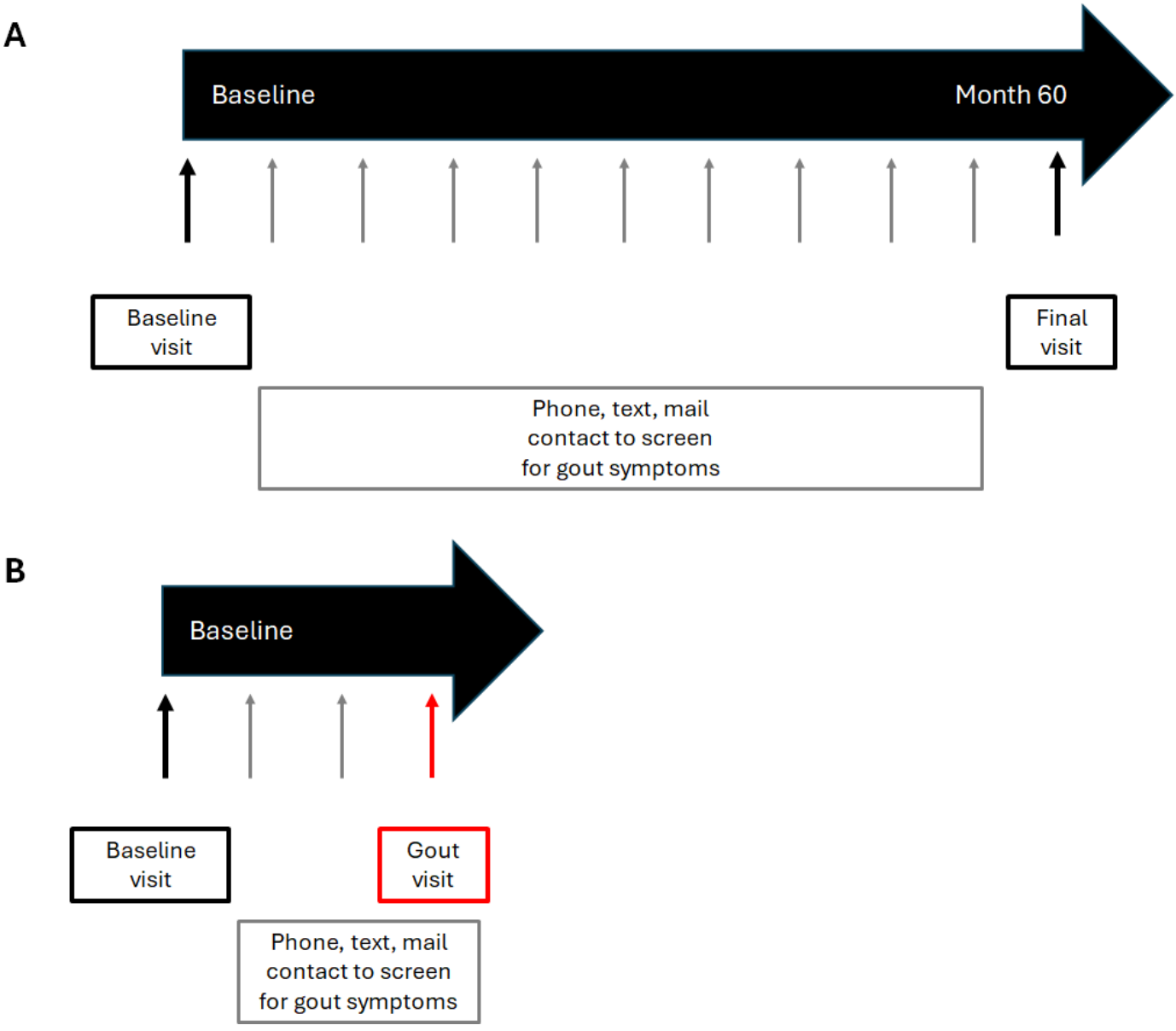

Figure 1 Flow of study participants and assessments throughout the study. (A) Study flow for a participant who does not develop gout over the 5-year follow-up. After the baseline visit, participants are contacted every 6 months by phone, text or mail to screen for gout symptoms. If they have not developed gout according to the 2015 American College of Rheumatology/European Alliance of Associations for Rheumatology gout classification criteria over 5 years, they are invited to attend the final study visit at month 60 and exit the study. (B) Study flow for a participant who develops gout during the 5-year follow-up (this example shows gout developing 18 months after the baseline visit). After the baseline visit, participants are contacted every 6 months by phone, text or mail to screen for gout symptoms. If they develop gout according to the 2015 ACR/EULAR gout classification criteria, they are invited to attend the gout study visit and exit the study.

(using the European Quality of Life (EuroQoL) questionnaire),[28] hyperuricemia-related illness perception (using a hyperuricemia-specific Brief Illness Perceptions Questionnaire),[29] beliefs about medicines (using the Beliefs about Medicines Questionnaire),[30] body pain and foot pain over the past week (using 100 mm pain visual analogue scales), foot pain location over the past week using the Chatterton Foot Pain Diagrams,[31] foot pain and disability using the Manchester Foot Pain and Disability Index (MFPDI)[32] and activity limitation using the Health Assessment Questionnaire—II (HAQ-II).[33]

Blood samples are sent for laboratory analysis to determine serum creatinine and C reactive protein (CRP). Whole blood, serum and urine samples are also collected and stored if participants consent to genetic testing. For those participants who agree to genetic testing, candidate gene analysis for the progression from asymptomatic hyperuricemia to gout includes several dozen genes at loci associated with gout but not with serum urate.[34] Baseline serum is stored and following recruitment of all study participants, samples will be tested for soluble mediators of gout-related inflammation including IL-1β

by ELISA (a central cytokine implicated in initiation of the gout flare).[35]

Bilateral plain weight-bearing anterior–posterior radiographs of the feet are obtained at the baseline visit and are deidentified and scored by a central reader who is blinded to baseline and follow-up data. Metatarsophalangeal joints 1–5 and the hallux interphalangeal joint are assessed for osteoarthritis using the Kellgren and Lawrence criteria[36] and for erosion and joint space narrowing according to the Sharp-van der Heijde scoring system, modified for gout.[37]

Finally, the baseline evaluation includes a musculoskeletal ultrasound scan within 2 weeks of the study visit according to a standardised protocol (described below).

Six-month assessments

Participants are contacted by phone, mail, email and/or text message every 6 months for 5 years to determine whether they have developed symptoms of new joint pain or swelling. Participants reporting symptoms suggestive of gout are screened against the 2015 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) gout classification criteria.[38] If gout is suspected, then a gout development visit is scheduled. If the participant does not fulfil the criteria, they continue in the study.

In addition, participants are asked to report any new medical problems during the 6-month assessments, including specific cardiovascular events (myocardial infarction, myocardial revascularisation, heart failure, atrial fibrillation, angina, chest pain, stroke and transient ischaemic attack, and peripheral artery surgery-revascularisation including aortic aneurysms).[39] Any newly reported medical problems are confirmed through the participant's medical records. The primary diagnosis causing any new hospital admission is also recorded. Participants are asked to report any new medications, including initiation of any urate-lowering therapy, colchicine or other anti-inflammatory drugs (for indications other than gout) during the follow-up period.

Serum urate is not measured during these 6 monthly assessments. Therefore, fluctuations in serum urate between baseline and 5 years will not be captured. While this is a potential limitation, analysis of publicly available datasets has shown that repeat serum urate testing is not superior to a single measure of serum urate for prediction of incident gout over approximately one decade.[40]

Multiple (up to six) attempts are made to make contact at each time, 6-month time point. Each participant is asked to provide contact details of at least one person in their family in the event that the participant cannot be contacted. To minimise the impact of loss to follow-up, participants are also asked to consent to review of medical records. If participants agree to medical record review, attempts are made to capture development of gout through review of these records, in addition to the phone call assessments.

Participants also receive postcard, text message or email reminders every 3 months to contact the study co-ordinators if new symptoms develop between the 6-month assessments.

Gout development visit

If participants develop symptoms of new joint pain or swelling during the follow-up period and fulfil or possibly fulfil the 2015 ACR/EULAR classification of gout,[38] a further clinical study visit is undertaken within 2 weeks. The exact location(s) of new joint pain or swelling is marked on a homunculus diagram and a physical exam is undertaken as per the baseline visit (including assessment of BMI, waist circumference, blood pressure and the presence of tenderness and swelling using the 66/68 tender and swollen joint counts).[25] In addition, clinical risk factors are recorded as per the baseline visit and participants are asked to complete the EuroQoL questionnaire, 100 mm body pain and foot pain VAS, the Chatterton Foot Pain diagrams, MFPDI and HAQ-II. Blood samples are collected for serum urate, creatinine and CRP and whole blood, serum and urine samples are collected and stored as per the baseline visit for genetic testing if applicable. A repeat musculoskeletal ultrasound scan is also completed within 2 weeks of this visit. Investigators offer expert advice to participants' physicians about gout management as appropriate, but do not directly provide clinical care. Joint aspiration is not required to confirm gout for the purposes of this study.

Final study visit

At month 60, a final study visit is arranged and includes determining whether the participant has developed any new joint pain or swelling since the last contact, or any new medical problems, cardiovascular events or hospital admissions. As per the baseline visit, a physical exam is undertaken, and clinical risk factors are recorded. Participants are asked to complete the EuroQoL questionnaire, 100 mm body pain and foot pain VAS, the Chatterton Foot Pain diagrams, MFPDI and HAQ-II. Blood samples are collected for serum urate, creatinine and CRP and whole blood, serum and urine samples are collected and stored as per the baseline visit if applicable. A repeat ultrasound scan is also performed within 2 weeks of the study visit. Multiple (up to six) attempts are made to arrange the final follow-up visit.

Ultrasound assessment

For this study, ultrasound has been selected as the advanced imaging method (in preference to dual energy CT) due to lack of ionising radiation, widespread availability and ability to assess both urate crystal deposition and joint inflammation.[41] The ultrasound assessment involves a bilateral scan of the first and second metatarsophalangeal joints and knees as well as patellar and Achilles tendons. Double contour, erosion and synovitis are assessed at the first and second metatarsophalangeal joints and knees. Tophus is assessed at the patellar and

Achilles tendons as well as intra-articularly at the first and second metatarsophalangeal joints and knees. Aggregates are assessed at only the patellar and Achilles tendons.

Elementary gout lesions are assessed according to definitions proposed by the Outcomes in Rheumatology (OMERACT) ultrasound group[9 42] and scored according to the OMERACT gout ultrasound scoring system.[43] The following elementary lesions are assessed and scored:

1. **Double contour** (graded semiquantitative, 0=absent, 1=possible, 2=definite but minimal, 3=definite and severe): 'abnormal hyperechoic band over the superficial margin of the articular hyaline cartilage, independent of the angle of insonation and which may be either irregular or regular, continuous or intermittent and can be distinguished from the cartilage interface sign'.[9 42]
2. **Tophus** (graded semiquantitative, 0=absent, 1=possible, 2=definite but minimal, 3=definite and severe): 'a circumscribed, inhomogeneous, hyperechoic and/or hypoechoic aggregation (which may or may not generate posterior acoustic shadow), which may be surrounded by a small anechoic rim'.[9 42]
3. **Aggregate** (graded semiquantitative, 0=absent, 1=possible, 2=definite but minimal, 3=definite and severe): 'bright hyperechoic, isolated spots too small to fulfil the tophus definition and characterised by maintaining their high degree of reflectivity when the insonation angle is changed'.[43] Although in the OMERACT definitions, it was specified to score aggregates only in people with proven gout when other ultrasound gout lesions were also present,[43] the steering committee decided to include aggregates in the ultrasound protocol, noting that study participants are at increased risk of gout.
4. **Erosion** (graded binary, 0=absent, 1=present): 'an intra-articular and/or extra-articular discontinuity of the bone surface (visible in two perpendicular planes)'.[9 42]

In addition, the following lesions are also recorded to capture the presence of synovitis:

5. **Synovitis score** (graded semiquantitative, 0=none, 1=minimal, 2=moderate, 3=severe): using a composite score of power Doppler signal and grey scale hyperplasia (which are also scored separately) using the OMERACT EULAR definition.[44]

Representative images for each grade are made available in an imaging atlas to standardise scoring of the ultrasound lesions across sites. Recent reliability work undertaken by the OMERACT Ultrasound working group has shown good intra-rater and inter-rater reliability for the semiquantitative scoring system and sensitivity to change over time.[43 45]

The first metatarsophalangeal joint is scanned from the dorsal and medial aspects with the joint in a neutral position. A lesion is considered present if observed at either the dorsal or medial aspect and the lesion with the highest grade is recorded. The second metatarsophalangeal joint is scanned from the dorsal aspect. The dorsal aspect of the knee is examined in a flexed position (at least 90° according to the capability of the examined participant to flex completely the knee). The patellar and Achilles tendons are assessed for aggregates by scanning the distal, middle and proximal portions of the tendons. The aggregates can only be scored in a participant if other ultrasound features suggestive of gout (double contour and/or tophus) is present/has previously been present in that participant and if the aggregates are not located inside a tophus. Aggregates are considered present if observed at any portion of the tendon. However, the portion(s) of the tendon in which the aggregates are observed are also recorded.

Ultrasound examinations across the sites are performed at baseline and at month 60 (or earlier if the participant develops gout during the follow-up period). All ultrasound examinations are performed by an experienced musculoskeletal sonographer who is independent of the researchers who interact with the participants at the study visits. Each site uses a high-end ultrasound machine at each examination point. Ultrasound scans are read locally on a standardised ultrasound report form, with images at each joint/tendon area recorded for documentation and quality control. The participants and clinical investigators are blinded to the ultrasound scores. The machine, probe frequency and sonographer experience/training are recorded on the ultrasound assessment report form.

The primary analysis will be a combined semiquantitative double contour-tophus (SQDT) sum score[45] with exploratory/sensitivity analysis for each lesion separately (double contour, tophus, erosion, aggregates and also synovial hypertrophy and Doppler) and additional combinations. For a sensitivity analysis to ensure consistency across sites, the images and reports will be viewed and rescored by a single central reader, who is blinded to all clinical details including gout outcomes. The primary analysis will, however, be performed on images scored at each of the sites to best reflect 'real-world' clinical imaging practice.

Patient and public involvement

There was no patient or public involvement in the design of this research.

Sample size calculation

A computed sample size of 904 was originally estimated to allow analysis of significant transition from hyperuricemia to symptomatic gout and assumed a 5-year incidence of gout of 9.9%.[3] The original study intent was to determine whether there was significant increased odds of developing gout in those with MSU crystal deposition compared with those without. The influence of the global COVID pandemic on study site and participant recruitment, a reappraisal in light of a continuous ultrasound scoring system of MSU crystal deposition that has now been validated[43 45] and can be used in the analysis, and the observation that the incidence of gout in the cohort to date is higher than anticipated (as at 21 March 2024,

11.8% (95% CI 8.3 to 16.5) with an average of 2.4 years follow-up) has necessitated an amendment of the study methods of analysis and sample size justification blinded to the MSU crystal deposition status of the participants. Importantly this amendment has been informed by the overall rate of gout observed in the study cohort but did not include analysis of MSU crystal deposition data.

Pragmatically, recruitment will be completed with approximately 250 participants of whom 28 are known to have gout with an average follow-up of 2.4 years (range 0.01–4.61 years). Additional cases of gout are assumed to continue to accrue at the same rate as observed in the study to date that is, 4.9 (95% CI 3.3 to 7.0) new classifications of gout per 100 patient years of follow-up. It is anticipated that the total proportion of participants who have developed gout in 5 years will have increased to 23% (58 participants develop gout overall).

A sample of 58 participants with gout and 192 (ie, total n=250) without gout achieves 90% power to detect a difference of 0.14 between the area under the receiver operating curve (ROC) curve (AUC) under the null hypothesis of 0.50 and an AUC under the alternative hypothesis of 0.64 using a two-sided z-test at a significance level of 0.050. The data are continuous responses. The AUC is computed between false-positive rates of 0.00 and 1.00. The ratio of the SD of the responses in the negative group to the SD of the responses in the positive group is 1.00. (PASS 16 Power Analysis and Sample Size Software (V.2018). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.) A difference in AUC of 0.18 (ie, AUC ROC curve for MSU crystal deposition=0.68) could be detected with a 12% incidence of gout. A total of 58 participants with gout would enable multivariable analysis with at most six independent variables (rule of thumb that 10 events are required per independent variable) to be performed.

Data analysis plan

Analysis of follow-up data: primary analysis

The primary aim of this study is to determine whether those people who already have an increased risk of gout due to elevated serum urate concentrations (ie, serum urate (≥8 mg/dL) at baseline visit are at additional increased risk of developing gout (according to the 2015 ACR/EULAR criteria) over 5 years if they have evidence of increased MSU crystal deposition.

The primary analysis will focus on follow-up data. The development of gout will be examined using standard logistic regression techniques (Proc Logistitic, SAS V.9.4, SAS Institute) and time-dependent methods (https://www.lexjansen.com/nesug/nesug06/an/da29.pdf) to estimate the discriminability of ultrasound evidence of MSU crystal deposition (as a continuous variable) to predict the presence/absence or time to the development of gout using a standard ROC approach with the results expressed as AUC with 95% CI and tested to determine whether the observed AUC differs from that attributable to chance (ie, AUC >0.50). The model will include study site stratification in a secondary analysis. Optimal cut-off points for MSU crystal deposition score (and its components) that are likely to be of clinical relevance will be determined from investigation of sensitivity/specificity at each score (Youden's index).

The primary analysis will analyse gout as defined by the 2015 ACR/EULAR gout classification criteria. In a sensitivity analysis, participants who are lost to follow-up but have gout documented in medical records or gout medications dispensed will be included in the analysis of gout cases, and a separate analysis using central reading ultrasound scores of MSU deposition in cases of disagreement with local reader scores.

Additional preplanned exploratory analyses will investigate whether baseline clinical, biochemical, health psychology and genetic variables predict gout either alone or in combination, and whether any of these variables alone or in combination are additive to the discriminability (if any) of the combined SQDT sum score.

Multivariable linear regression analysis will also be used to determine the independent predictors of change (end of study-baseline) in OMERACT ultrasound score. Following best practice, the choice of independent variables will not be on the basis of bivariate comparisons nor iterative model building techniques, rather models will be constructed based on expert clinical knowledge of likely associations. Standard multivariable regression techniques (including least absolute shrinkage and selection operator methods) will be used. Since these models are considered hypothesis generating, the final model choice will be on the basis of biological plausibility, parsimony and parsimony and goodness of fit.

Analysis of baseline data

Following recruitment of all participants into the study, analysis of the baseline data will proceed. This will include a description of baseline ultrasound findings and associations between clinical and ultrasound results. This project represents the largest imaging study of hyperuricemia ever reported and provides important information about the prevalence of ultrasound features of crystal deposition in hyperuricemia, and associated features (including comorbid illness, features of joint damage on plain radiography, health-related quality of life and activity limitation).

Baseline analysis will also include a descriptive analysis of the perceptions about hyperuricemia questionnaire, which includes participants' perceptions about elevated serum urate levels, concerns about associated comorbid conditions and willingness to take medicines to reduce serum urate levels (this information will inform future development of intervention studies for hyperuricemia).

In participants who have consented to genetic testing, the impact of genetic variants of gout-associated genes on MSU crystal deposition in the presence of hyperuricemia will be explored, including *ABCG2* genotype. *ABCG2* is strongly associated with gout, and these effects are not completely explained by the effects of *ABCG2* on serum

urate levels (reviewed in Cleophas *et al*).[46] *ABCG2* may also contribute to gout through deposition of MSU crystals within the joint, or by regulating the inflammatory response to deposited crystals.

ETHICS AND DISSEMINATION

This study has been approved by the New Zealand Ministry of Health Southern Health and Disability Ethics Committee (MEC/05/10/130AM16) and by the local IRB for each participating centre. A detailed participant information sheet is provided, and participants are required to sign an informed consent form prior to inclusion in the study. Genetic testing is optional and not required for inclusion into the study. Expert advice regarding treatment and management of gout is given to the general practitioners of participants who develop gout during the study. The confidentiality of recruited participants is ensured at all times.

The results from the study will be disseminated via peer-reviewed journal articles and national and international conference presentations. The results will also be made available by electronic and postal mail to participants.

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Contributors Conception and/or design of the study: SS, GG, WJT, TM, BM, AH, IS, LS, TP, MA, M-LP-G, TN, EN, JVM, JDFG, LT, HBH, TU, M-ADA, JM, MS, CL, ND. Drafting the work: SS, ND. Revising the work for important intellectual content: GG, WJT, TM, BM, AH, IS, LS, TP, MA, M-LP-G, TN, EN, JVM, JDFG, LT, HBH, TU, M-ADA, JM, MS, CL. Approved the final version to be published: SS, GG, WJT, TM, BM, AH, IS, LS, TP, MA, M-LP-G, TN, EN, JVM, JDFG, LT, HBH, TU, M-ADA, JM, MS, CL, ND. Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: SS, GG, WJT, TM, BM, AH, IS, LS, TP, MA, M-LP-G, TN, EN, JVM, JDFG, LT, HBH, TU, M-ADA, JM, MS, CL, ND. The guarantor of the study is Nicola Dalbeth, who accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests ND has received consulting fees, speaker fees or grants from AstraZeneca, Novartis, Horizon, Selecta, Arthrosi, JW Pharmaceutical Corporation, PK Med, LG Chem, JPI, PTC Therapeutics, Protalix, Unlocked Labs, Hikma, Dexcel Pharma, Shanton Pharma, Sobi, Avalo outside the submitted work. MA reports a research grant from Grunenthal and meeting attendance support from Olatec outside the submitted work. LT has received consulting or speaker fees from Janssen, Pfizer, Novartis, UCB, and GE Healthcare outside the submitted work. TN has received consulting fees from Sobi, Horizon/Amgen outside the submitted work. EN has received speaker fees or other support from STADA, Sandoz, Egis Pharmaceuticals and AbbVie outside the submitted work. HBH has received consulting fees from AbbVie, Lilly, Novartis, and UCB outside the submitted work. M-AD'A has received consulting fees, speaker fees or grants from AbbVie, Novartis, UCB, Janssen, Galapagos, Pfizer, Amgen, AstraZeneca, GSK outside the submitted work. The other authors report no conflicts.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by New Zealand Ministry of Health Southern Health and Disability Ethics Committee (MEC/05/10/130/AM16). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; internally peer-reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study.

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