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Perceptions about asymptomatic hyperuricemia and views about urate-lowering therapy in people with asymptomatic hyperuricemia

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Abstract

Background/Aims: Asymptomatic hyperuricemia is a precursor of gout and is also associated with cardiovascular disease and chronic kidney disease. The aim of this study was to understand perceptions about asymptomatic hyperuricemia and views about urate-lowering therapy in people with asymptomatic hyperuricemia.

Methods: Participants in a multi-national study of asymptomatic hyperuricemia completed questionnaires about their perceptions of hyperuricemia, concern about hyperuricemia-associated health conditions, and willingness to take urate-lowering medication. All had a screening serum urate of ≥0.48 mmol/L (8 mg/dL) and no current or previous symptoms of gout.

Results: Overall, participants perceived that hyperuricemia had no or very few consequences on their life. Dietary factors were the most reported cause, while 37% did not know the cause. Participants reported a wide range in concern about hyperuricemia and the risk of developing gout. Concern about the risk of developing kidney disease or cardiovascular disease was also highly variable but was higher than concern about elevated serum urate (P<0.001). Most did not think a urate-lowering medication was necessary and there was moderate concern about the long-term use of urate-lowering medication. Medication necessity beliefs were most strongly associated with whether participants were willing to take urate-lowering medication (partial R^2 =0.27, P<0.001).

Conclusions: Most participants perceived minimal consequences of asymptomatic hyperuricemia. Hyperuricemia was not well understood by participants, and biological causes were generally under-recognised. Despite a range of concerns about hyperuricemia-associated conditions, particularly kidney disease and cardiovascular disease, a urate-lowering medication for asymptomatic hyperuricemia was not considered necessary, which aligns with most current management guidelines.

Significance & Innovation

- Illness perceptions are key determinants of patients' behavior for managing health conditions Asymptomatic hyperuricemia is common and is a precursor to gout
- This study provides new insights into perceptions about hyperuricemia and views about urate-lowering therapy in people with asymptomatic hyperuricemia

Hyperuricemia (elevated serum urate level) is the necessary precursor for the development of gout [1 2] and is also associated with cardiovascular disease and chronic kidney disease [3 4]. Many factors contribute to serum urate concentrations, including genetic factors, kidney function, body mass index, dietary factors, and medications [5 6]. There is a strong concentration-dependent relationship between serum urate and development of gout, with a hazard ratio of >60 for the highest concentrations of serum urate [2]. Currently, urate-lowering therapy is not recommended for asymptomatic hyperuricemia [7], and most people with hyperuricemia have no symptoms and do not develop gout [2].

Illness perceptions are key determinants of patients' behavior for managing health conditions and have been associated with important outcomes in chronic diseases [8]. When faced with a new health threat individuals will actively construct a mental representation of the illness and this guides their behavior to manage the condition, such as engagement with treatment [9]. Research suggests that it is difficult for individuals to conceive of illnesses without symptoms and consider such symptom-less illnesses to be a serious threat to health [10 11].

Perceptions of the benefits and concerns about medication are also important factors in patients' acceptance and adherence to new treatment regimens. Perceptions of the necessity of the medicine, as well as concerns

about potential adverse effects, strongly influence a person's willingness to initiate and maintain a prescribed therapy [12]. Studies suggest that individuals who view medications as essential for managing their condition are more likely to adhere, whereas those with concerns about dependency or side effects exhibit lower adherence and persistence with the treatment [13].

While many studies have examined patient perceptions about gout, perceptions of asymptomatic hyperuricemia have not been reported. This is a relevant question as asymptomatic hyperuricemia is common [14] and can progress to gout. The aim of this study was to understand perceptions about asymptomatic hyperuricemia and views about urate-lowering therapy in people with asymptomatic hyperuricemia.

Methods

This was a pre-specified analysis of baseline data from the Transitions in Gout Research (TIGER) study. The TIGER study is a five-year international multicenter prospective cohort study designed to understand risk factors for development of gout in people with asymptomatic hyperuricemia. The study has been registered (ACTRN12619000915156) and the full study protocol has been published [15].

In brief, TIGER study participants were recruited from June 2019 to August 2024 at study sites in Aotearoa New Zealand (three sites), France, Spain, Lithuania, USA, China, and Mexico. Participants were recruited from primary and secondary care settings, by public advertising, and through community pathology collection centres. All participants had a screening serum urate of ≥ 0.48 mmol/L (8 mg/dL); had no current or previous clinical symptoms of gout; and were aged between 18 and 80 years. The key exclusion criteria were: CKD4 or worse; other forms of inflammatory arthritis; serious illness with poor prognosis less than five years; previous synovial fluid analysis showing MSU crystals; clinically evident tophi; taking urate lowering therapy, canakinumab, or colchicine. This study was 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 center. All participants provided written informed consent.

All participants completed a baseline visit at the study site. The baseline visit included recording of demographic data, clinical risk factor assessment and physical examination including body mass index and waist circumference. Current medications and health conditions were recorded, including those documented in the modified-Rheumatic Disease Comorbidity Index (mRDCI) [16]. Participants also completed 100 mm pain visual analogue scales (VAS) for pain over the last week and global assessment of health. Laboratory tests were taken for measurement of serum creatinine, and eGFR was calculated according to the 2021 CKD-EPI creatinine equation [17].

At the baseline visit, participants also completed a hyperuricemia-specific brief illness perceptions questionnaire (BIPQ) [18]; as urate-lowering therapy use was an exclusion, the treatment control item in the BIPQ was not included. Participants also were asked about their concern about hyperuricemia-associated health conditions (gout, kidney disease, and cardiovascular disease, 0-10 Likert scale) and completed the beliefs about medicines questionnaire (BMQ) [19] subscales which assessed their views about medicines in general, and two questions about their specific views about taking medications to reduce serum urate (0-10 Likert scale): "How much do you feel you need medication to reduce your urate level?" and "How concerned are you about the long-term use of a medicine to reduce your urate level?". To assess how willing the person would be to take a medication to reduce their serum urate we asked: "How agreeable would you be to taking a medication to reduce your urate level?" (0-10 Likert scale, 0=not at all agreeable, 10= extremely agreeable). All questionnaires were translated and completed in the local language.

The current analysis was a descriptive and exploratory (hypothesis generating) cross-sectional study, as a specific hypothesis was not tested and inferential analysis was not the main objective. Given the low missing data rate, complete case analysis / listwise deletion was used throughout. Data from all participating sites were entered into a central database at the coordinating site at the University of Auckland, New Zealand. Means with standard deviations (SD) and percentages were used to describe the demographic and clinical characteristics of participants. Medians with interquartile ranges (IQR) and percentages were used to

describe the results of the questionnaires. "Agreeable to take a medication to reduce serum urate" scores were modelled. Variables were selected for inclusion in the model using external clinical judgement based upon previous experience with each of the instruments to reduce the risk of overfitting and to avoid a completely P value driven model selection process. A further screening process to determine those variables with significant Spearman correlation with the prespecified dependent variable was performed to reduce the number of variables in the model and iterative stepwise regression was then performed to optimize the order of inclusion of variables in the model since some collinearity was anticipated. Diagnostic plots, including plots of residual, normal probability plots and leverage plots were produced using the REG procedure of SAS and inspected to establish the goodness of fit of the model and that the residuals were normally distributed. Multicollinearity was assessed using the variance inflation factor. A variance inflation factor > 5 indicated multicollinearity [20]. The final model was reviewed for clinical and scientific relevance to determine whether *post hoc* inclusion of additional variables in the model was required, and the final model was selected on the basis of clinical relevance, parsimony and goodness of fit. Standardized beta coefficients were tabulated to enable comparison between variables. General linear modelling was used to compare concern between hyperuricemia-associated disease conditions. A significant main effect was reduced to pairwise comparisons with p adjusted using the method of Tukey to preserve an overall 5% significance level. The procedures of SAS (v 9.04 SAS Institute Inc, Cary, NC, USA) were used for these analyses.

Results

Participant characteristics

The cohort included 268 people with asymptomatic hyperuricemia who completed the BIPQ. None of the participants had a history of arthritis or clinical evidence of synovitis or subcutaneous tophi at the time of the baseline study visit. The clinical features of these individuals are shown in Table 1. Participants were predominantly men, with mean age 48 years and mean body mass index 30.5 kg/m^2. Pain scores were low and global assessment of health was high. Mean serum urate concentration was 0.52 mmol/L (8.7 mg/dL).

Perceptions about hyperuricemia

Overall, participants perceived that hyperuricemia had no or very little consequences on their life, and the presence of hyperuricemia had little emotional impact (Table 2). There was wide variation in participants' perceptions of chronicity and personal control, and concern about elevated serum urate levels.

Participants tended to report low understanding about hyperuricemia. Dietary factors were the most reported factor believed to cause elevated serum urate levels, while 37% described that the cause of their hyperuricemia as unknown. Genetic factors were believed to be the most important cause in 8.9% of participants.

Consistent with concern about elevated serum urate levels, participants reported a wide range in concern about the risk of developing gout (Table 2). There was similar concern about hyperuricemia and the risk of developing gout (*post hoc* Tukey P=0.11). Concern about the risk of developing kidney disease or cardiovascular disease was also highly variable but was higher than concern about hyperuricemia (*post hoc* Tukey P<0.001 for both kidney disease and cardiovascular disease).

Views about medications to reduce serum urate levels

Generally, participants viewed medications positively (Table 2). Most did not think that they needed a medication to reduce their serum urate and there was moderate concern about the long-term use of such a medication. There was a highly variable response about whether they were agreeable to take a medication to reduce the serum urate with median (IQR) score 5 (2, 8) (Figure 1).

In bivariable analysis, willingness to take a medication to reduce the serum urate associated with concern about hyperuricemia and risk of developing hyperuricemia-associated health conditions (gout, kidney disease, and cardiovascular disease), perceived need to take a medication to reduce the serum urate, beliefs about medicines, and comorbidities (Table 3). In multivariable analysis, the perceived need for medication to reduce serum urate was most strongly associated with whether participants were agreeable to take urate-lowering medication (R^2 =0.27, P<0.001, Table 4). In addition, beliefs about the harms and benefits of

medicines, the Modified-Rheumatic Disease Comorbidity Index, and concern about hyperuricemia were significantly associated (model cumulative R^2 =0.38, P<0.001). Sex or geographical region did not associated with willingness to take urate-lowering medications.

Discussion

This study provides novel insights into the views and experience of people with asymptomatic hyperuricemia. Consistent with an asymptomatic condition, participants reported low scores for the consequences, symptoms, and emotional response domains of the hyperuricemia-specific BIPQ. There was a broad range of concern about hyperuricemia and hyperuricemia-associated conditions including gout, kidney disease and cardiovascular disease. Participants did not consider that a urate-lowering medication was needed, which is consistent with most current international management guidelines.

As reported in our prior studies of gout, dietary factors were considered the most important factor causing asymptomatic hyperuricemia [21-24]. More than one third of participants did not know the cause, and fewer than 10% of participants reported that genetic factors were the most important factor. Biological causes such as genetic variants, kidney function and body composition were generally under-recognised, in contrast to the scientific literature which shows that these factors play a central role in serum urate regulation [5 6 25 26]. These findings highlight the ongoing gap of translating scientific discoveries to community understanding about hyperuricemia and gout.

The study provides insights into personal decisions about taking medications, particularly for an asymptomatic laboratory finding. Our findings indicate the importance of patient perceptions about the need for such a medication. In the context of asymptomatic hyperuricemia, there is some evidence that incident gout can be prevented with urate-lowering therapy [27], but no compelling evidence for prevention of kidney disease progression [28-30] or cardiovascular disease [27]. Study participants reported low necessity beliefs about urate-lowering medication, which is consistent with current evidence and management guidelines.

Collectively, these data indicate that much more compelling evidence would be needed for people with asymptomatic hyperuricemia to adopt urate-lowering medication.

Our findings about willingness to take urate-lowering therapy for asymptomatic hyperuricemia align with numerous studies that reported that beliefs about the necessity of treatment is a strong predictor of medication adherence in long-term symptomatic health conditions [13]. The results suggest that it would be difficult for individuals to take long term medication for asymptomatic hyperuricemia as the condition elicits a low level of concern and perceived consequences. Moreover, the treatment is seen as not essential and people with asymptomatic hyperuricemia have moderate concern for taking medication for the condition long term.

Study strengths include the well characterised multi-national cohort, with consistent phenotyping and data collection. It should be noted that the study findings may not be generalisable to all people with asymptomatic hyperuricemia, as the study participants were volunteers in a cohort study of asymptomatic hyperuricemia and may have had different perceptions and health concerns to those not volunteering for the study. Additionally, this was a cross-sectional study and hypothetical views about taking a medication in the context of a research questionnaire may not translate to medication adherence in real-life.

In summary, most people with asymptomatic hyperuricemia report no or very few self-identified consequences of this laboratory finding. Asymptomatic hyperuricemia is not well understood, and biological causes are generally under-recognised by people with asymptomatic hyperuricemia. Despite a range of concerns about hyperuricemia-associated conditions, particularly kidney disease and cardiovascular disease, a urate-lowering medication was not considered necessary by individuals with asymptomatic hyperuricemia, which is in line with most of the current management guidelines regarding asymptomatic hyperuricemia.

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Table 1. Clinical features of participants. Unless specified, data are presented as mean (SD).

Clinical feature (n=268)		
Age, years	48 (18)	
Male sex, n (%)	218 (81%)	
Ethnicity, n (%)	African/Black	5 (1.9%)
	East Asian	65 (24.3%)
	Hispanic	10 (3.7%)

	Māori	11 (4.1%)
	Pacific Island	19 (7.1%)
	South Asian	36 (13.4%)
	White	112 (41.8%)
	Other Indigenous	1 (0.4%)
	Other/unknown	9 (3.4%)
Country of residence	New Zealand	144 (53.7%)
	China	64 (23.9%)
	France	21 (7.8%)
	Spain	21 (7.8%)
	Mexico	10 (3.7%)
	Lithuania	8 (3.0%)
Hypertension, n (%)	109 (40.7%)	
Cardiovascular disease*, n (%)	58 (22%)	
Type 2 diabetes, n (%)	34 (12.7%)	
eGFR < 60 mL/min/1.73m$^{2`}$	38 (15%)	
eGFR, mL/min/1.73m^2	90.4 (25.2)	
Modified-Rheumatic Disease Comorbidity Index	2.38 (2.20)	
Units of alcohol/day	4.2 (7.6)	
Units of beer/day	1.9 (5.2)	
Aspirin use, n (%)	23 (8.6%)	
Diuretic use, n (%)	44 (16.4%)	
Body mass index, kg/m^2	30.5 (6.5)	
Waist circumference, cm	103.3 (15.6)	
Pain score, mm	12.0 (21.4)	
Patient global assessment of health, mm	81.1 (16.3)	
Serum urate, mmol/L	0.52 (0.04)	
Serum creatinine, µmol/L	91.4 (26.3)	

*Includes chronic heart failure, peripheral vascular disease, myocardial revascularization, peripheral artery surgery revascularization (inc. aortic aneurysm), cardiac arrhythmia (atrial fibrillation/flutter), angina, myocardial infarction or stroke

Table 2. Perceptions about hyperuricemia, beliefs about medicines in general, and views about medications to reduce serum urate. Unless specified, data are presented as median (25th-75th percentile range).

Brief hyperuricemia perception questionnaire	
Consequences (10=severely affects life)	0 (0, 2)

Timeline (10=will continue forever)	4 (2, 7)
Personal control (10=extreme amount)	5 (2, 6)
Symptoms (10=severe symptoms)	0 (0, 1)
Concern (10=extremely concerned)	5 (2, 7)
Understanding (10=very clearly)	4 (1, 7)
Emotional response (10=extremely affected)	1 (0, 3)
Most important factor believed to cause hyperuricemia	
Dietary factors, n (%)	102 (38%)
Unknown, n (%)	100 (37%)
Genetic factors, n (%)	24 (8.9%)
Overweight, n (%)	18 (6.7%)
Medications, n (%)	7 (2.6%)
Kidney disease, n (%)	7 (2.6%)
Other health condition, n(%)	7 (2.6%)
Lack of exercise, n (%)	3 (1.1%)
Other, n(%)	2 (0.7%)
Concern about hyperuricemia-associated health conditions	
Concern about risk of developing gout (10=extremely concerned)	5 (3, 8)
Concern about risk of developing kidney disease (10=extremely concerned)	6 (3, 9)
Concern about risk of developing cardiovascular disease (10=extremely concerned)	6 (3,9)
Beliefs about medicines questionnaire - general subscales	
Harm subscale (maximum score 20)	9.5 (9, 12)
Overuse subscale (maximum score 20)	12 (10, 14)
Benefit subscale (maximum score 20) *	16 (15, 18)
Views about using medication to reduce serum urate	
Need to take medication to reduce serum urate (10=essential)	2 (0, 5)
Agreeable to take a medication to reduce serum urate (10= extremely agreeable)**	5 (2, 8)
Concern about the long-term use of a medication to reduce serum urate (10=extremely concerned)	6 (2, 8)

*Missing beliefs about medicines benefit questions from one site (n=247 for this variable)
**Responses available from 258 participants.

Table 3. Correlations between agreeable to take a medication to reduce serum urate scores and other variables.

Variables	Spearman r (95% CI) p
Age	0.08 (-0.04, 0.20) p=0.18
Sex	0.04 (-0.09, 0.16) p=0.56
Serum urate level	0.03 (-0.15, 0.10) p=0.68
Modified-Rheumatic Disease Comorbidity Index	**0.24 (0.12, 0.35) p<0.0001**
Brief hyperuricemia perception questionnaire	
Consequences (10=severely affects life)	0.02 (-0.10,0.14) p=0.74
Timeline (10=will continue forever)	0.06 (-0.07, 0.18) p=0.37
Personal control (10=extreme amount)	-0.002 (-0.13, 0.12) p=0.98
Symptoms (10=severe symptoms)	0.05 (-0.07, 0.18) p=0.37
Concern (10=extremely concerned)	**0.17 (0.05, 0.29) p=0.0061**
Understanding (10=very clearly)	0.08 (-0.04, 0.20) p=0.21
Emotional response (10=extremely affected)	0.04 (-0.08, 0.16) p=0.51
Concern about hyperuricemia-associated health conditions	
Concern about risk of developing gout (10=extremely concerned)	**0.22 (0.09, 0.33) p=0.0006**
Concern about risk of developing kidney disease (10=extremely concerned)	**0.22 (0.11, 0.34) p=0.0003**
Concern about risk of developing cardiovascular disease (10=extremely concerned)	**0.24 (0.12, 0.35) p=0.0001**
Beliefs about medicines questionnaire - general subscales	
Harm subscale (maximum score 20)	**-0.28 (-0.39, -0.16) p<0.0001**
Overuse subscale (maximum score 20)	**-0.15 (-0.28, -0.03) p=0.015**
Benefit subscale (maximum score 20)	**0.30 (0.18, 0.41) p<0.0001**
Views about medications to reduce serum urate	
Need to take medication to reduce serum urate (10=essential)	**0.45 (0.34, 0.54) p<0.0001**
Concern about the long-term use of a medication to reduce serum urate (10=extremely concerned)	0.02 (-0.11, 0.14) p=0.80

Table 4. Stepwise linear regression model to determine variables associated with agreeable to take a medication to reduce serum urate scores. All variables with p<0.05 in the bivariate correlation analysis shown in Table 3 were included in the model.

Variable	ß-coefficient	SE	Standardized ß-coefficient	95% Confidence Limits		t value	P	Partial R^2	Cumulative R^2	VIF
Perceived need for medication to reduce urate	0.497	0.066	0.419	0.366	0.627	7.50	<.0001	0.270	0.270	1.152
Beliefs about medicines questionnaire-harm	-0.227	0.064	-0.202	-0.353	-0.101	-3.55	0.0005	0.059	0.329	1.193
Modified-Rheumatic Disease Comorbidity Index	0.205	0.084	0.132	0.043	0.370	2.45	0.015	0.017	0.346	1.069
Beliefs about medicines questionnaire-benefit	0.190	0.081	0.137	0.030	0.350	2.35	0.020	0.012	0.358	1.250
Brief hyperuricemia perception questionnaire-concern	0.157	0.058	0.149	0.041	0.272	2.68	0.008	0.019	0.377	1.145

The following variables were included in this model: Modified-Rheumatic Disease Comorbidity Index, brief hyperuricemia perception questionnaire-concern, concern about gout risk, concern about kidney disease risk, concern about heart disease risk, BMQ-harm, BMQ-overuse, BMQ-benefit, perceived need for medication to reduce urate.

Figure legends

Figure 1. Distribution of agreeable to take a medication to reduce serum urate scores (0=not at all agreeable, 10= extremely agreeable).

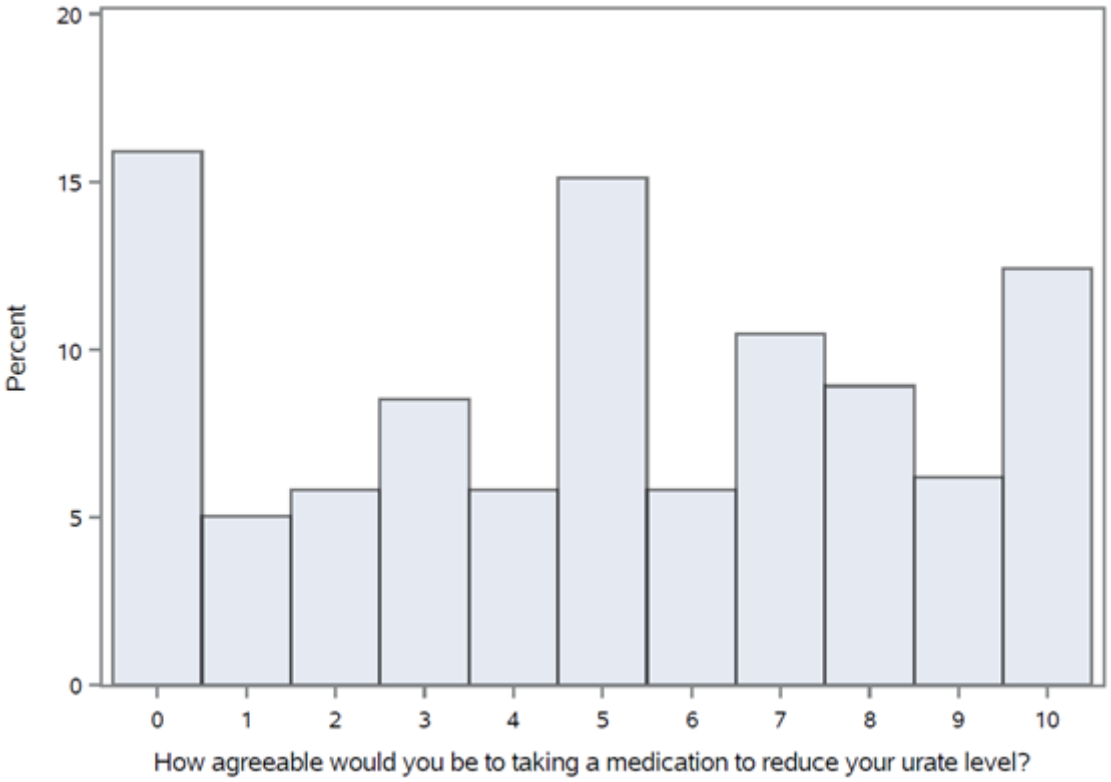

Figure 1 BIPQ TIGER paper.tif