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Ultrasound features of the first metatarsophalangeal joint in gout and asymptomatic hyperuricaemia: comparison with normouricaemic individuals

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ABSTRACT

Objective. The first metatarsophalangeal joint (1MTPJ) is frequently affected in gout. The aim of this study was to identity ultrasound features of the 1MTPJ in people with gout and people with asymptomatic hyperuricaemia compared with normouricaemic controls.

Methods. Participants with gout (n=23), asymptomatic hyperuricaemia (n=29) and age- and sex-matched normouricaemic control participants (n=34) underwent a grey-scale and power Doppler ultrasound assessment of bilateral 1MTPJs by a single musculoskeletal radiologist. No participants had clinical evidence of joint inflammation at the time of scanning. The static images were later read by two musculoskeletal radiologists for the presence of the double contour sign, tophus, erosion, effusion, synovial hypertrophy, synovitis and cartilage thickness.

Results. Compared to normouricaemic control participants, participants with gout and participants with asymptomatic hyperuricaemia had more frequent double contour sign (odds ratio (OR) 3.91, *P*=0.011 and OR 3.81, *P*=0.009, respectively). Participants with gout also had more erosion (OR 10.13, *P*=0.001) and synovitis (OR 9.00, *P*<0.001) and had greater tophus and erosion diameters (*P*=0.035 and *P*<0.001, respectively). More severe erosion and synovitis grades and a less severe effusion grade were independently associated with gout compared with asymptomatic hyperuricaemia ($R^2 = 0.65$, $p < 0.001$).

Conclusion. Urate deposition, synovitis and bone erosion are common at the 1MTPJ in people with gout, even in the absence of flare. Although individuals with asymptomatic hyperuricemia lack ultrasound features of inflammation or structural joint changes, they demonstrate a similar frequency of urate deposition.

SIGNIFICANCE AND INNOVATIONS

- Ultrasound features of urate deposition, soft tissue inflammation and bone erosion are common at the 1MTPJ in people with gout, despite the absence of clinical symptoms of acute arthritis.
- People with asymptomatic hyperuricemia lack features of inflammation and structural joint changes on ultrasound, but demonstrate a similar frequency of subclinical urate deposition.

Gout results from the formation and deposition of monosodium urate (MSU) crystals in structures of the musculoskeletal system in the presence of hyperuricaemia [1]. MSU crystals have the potential to initiate inflammatory responses resulting in painful episodes of arthritis [2, 3]. Although hyperuricaemia is required for the development of symptomatic gout, many individuals with hyperuricaemia are clinically asymptomatic [4].

Despite a similar level of urate concentration throughout the body, MSU crystal deposition and gout-related features have a certain propensity for the first metatarsophalangeal joint (1MTPJ). Most people with gout experience acute 1MTPJ arthritis at some point during the course of the disease [5]. Furthermore, people with gout report consistent 1MTPJ pain even after the resolution of clinical evidence of acute arthritis [6, 7]. The function of the 1MTPJ is also impaired in people with gout [8, 9]. It is unclear why gout has a predilection to affect the 1MTPJ, but may be associated with biomechanical loading or physical stress during the normal gait cycle [10, 11], or the co-occurrence of 1MTPJ osteoarthritis [12, 13].

High-resolution ultrasound has recently gained substantial interest in the assessment of individuals with gout due to its ability to visualise not only soft tissue inflammation (through its power Doppler capability) and joint damage, but also MSU crystal deposition. The ultrasound presence of MSU crystals along the surface of articular cartilage (the double contour sign) is the most well-recognised ultrasound feature in people with gout and has been included in the 2015 ACR/EULAR Gout Classification Criteria [14]. However, the double contour sign bears close resemblance to bone interface reflections frequently seen in healthy joints, which increases the rate of false-positives [15-17]. The double contour sign has also been observed in individuals with asymptomatic hyperuricaemia [18-21]. Despite this evidence of crystal deposition in people with asymptomatic hyperuricaemia, very few

studies have systematically assessed for features of soft tissue inflammation and joint damage in this population [20-22]. The aim of this study was to identity ultrasound features of the 1MTPJ in people with gout and people with asymptomatic hyperuricaemia by comparing them with healthy normouricaemic controls.

PATIENTS AND METHODS

Participants

Participants with gout were recruited from Auckland District Health Board, New Zealand. All participants fulfilled the 1977 preliminary American Rheumatism Association (ARA) classification criteria for gout [33]. Participants without gout were recruited from Auckland University of Technology (AUT) staff. Participants without gout underwent serum urate capillary testing on the day of the study using a Reflotron® Plus (Roche Diagnostics Ltd., New Zealand) and were stratified into either the asymptomatic hyperuricaemic group (serum urate $\geq$6.9mg/dL) or the normouricaemic control group (serum urate <6.9mgl/dL). The three groups were age-and sex-matched. Participants were excluded if they were aged under 20 years; had a history of other inflammatory arthritis; were experiencing acute arthritis at the time of the study; had foot and/or ankle surgery in the previous three months; had a history of 1MTPJ surgery; or lower limb amputation. Ethical approval for the study was obtained from the AUT Ethics Committee (13/100). All participants provided written informed consent prior to data collection. Demographic data were obtained from all participants including age, gender, ethnicity, body mass index (BMI), current medications and medical history. Additionally, gout disease characteristics were documented for participants with gout including disease duration, flare history and tophus presence.

Ultrasound image acquisition

The ultrasound examination was performed at the AUT Horizon Scanning Clinic by a single experienced musculoskeletal radiologist (BA) who was blinded to all clinical features including gout status and serum urate results. A Phillips iU22 diagnostic ultrasound machine (Bothell, Washington, USA) with a 10 MHz, 55mm linear array transducer was used. Bilateral 1MTPJs were scanned with participants positioned supine with legs extended. A water-based gel was applied to the skin to optimise transducer-skin contact and to provide an acoustic interface. The dorsal, medial and plantar aspects of each joint were scanned using a multi-planar technique in which transverse and longitudinal planes were imaged. Each joint was maximally dorsiflexed and plantarflexed by the radiologist during scanning to ensure direct visualisation of the articular surfaces. Each joint was scanned in B-mode grey scale and then using power Doppler. Power Doppler involved the use of a standardised pulse frequency of 400 to 500 Hz and low wall filters with the gain adjusted to a level just below the disappearance of the colour signs under the bony cortex.

Ultrasound image interpretation

Two musculoskeletal radiologists (BA and RM) who were blinded to all clinical features, including gout status and serum urate results, and to each other's scores, independently reviewed the static images for eight ultrasound features: the double contour sign, tophus, erosion, effusion, snowstorm appearance, synovial hypertrophy, synovitis and cartilage thickness (defined in Supplementary Table 1). In accordance with previous research and the

Outcome Measures in Rheumatology group (OMERACT) recommendations, cartilage-related features (double contour sign and cartilage thickness) were assessed at the dorsal aspect of the 1MTPJ [23]. All remaining ultrasound features were assessed at the dorsal, medial and plantar aspects. The double contour sign, tophus and the snowstorm appearance were recorded as either present or absent at the 1MTPJ, while erosions, joint effusion, synovial hypertrophy and synovitis were graded using a four-grade semi-quantitative scale (grade 0=absent; grade 1=mild; grade 2=moderate; grade 3=severe) [24, 25]. For erosions, joint effusion and synovial hypertrophy the feature was considered present if graded $\geq$2 [24]. Synovitis was considered present if graded as $\geq$1 [25]. Additionally, the largest diameter of the largest tophus and erosion in each 1MTPJ was recorded using digital callipers. Thickness of the articular cartilage covering the dorsal first metatarsal head was also assessed by measuring the longest diameter using digital callipers [26].

Statistical Analysis

Demographic and medical data were described as mean (SD) for continuous data and frequency (%) for categorical data. The inter-reader reliability for the presence of each ultrasound feature was assessed using Cohen's kappa (k) in which values of 0 to 0.2 were considered poor; 0.2 to 0.4 fair; 0.4 to 0.6 moderate; 0.6 to 0.8 good; and 0.8 to 1.0 excellent [27]. The inter-reader reliability for cartilage thickness, tophus and erosion diameters and the severity grading for erosions, effusion, synovial hypertrophy and synovitis was assessed using intra-class correlation coefficients (ICC) which were interpreted using the following benchmarks: $\geq$0.75 excellent reliability; 0.40 to 0.75 fair to good reliability; and <0.40 poor reliability [28]. For the purpose of the inferential analyses, ultrasound feature

grades and thickness measures were calculated by taking the mean of the two readers. For dichotomous outcome measures (i.e. scored as either present or absent), the feature was considered present only if scored as present by both readers. For outcome measures assessed at dorsal, medial and plantar sites of the 1MTPJ, the maximum grade and thickness measures were used. Binary logistic regression was used to determine between-group differences for the presence of the double contour sign, tophus, erosion, effusion, snowstorm appearance, synovial hypertrophy and synovitis. Additionally, to determine between-group differences in grading of erosions, effusion, synovial hypertrophy and synovitis, multinomial regression with cumulative logit link was used. For the continuous outcome measures (tophus size, erosion size and cartilage thickness) linear regression models were used. All continuous outcomes were reviewed for normality using the residuals from a linear model with the participant group as the independent variable. All models accounted for repeated measures taken from right and left feet through using a mixed-models approach in which a participant-specific random effect and participant-nested random effect for foot-side were added to the model. This analysis produces results identical to an analysis of measures averaged for each foot-side that would allow for a between-foot-side correlation and also allows for any reweighting required due to missing values. Adjustments for gender, age, ethnicity and BMI, which were entered into each model simultaneously, were considered only if their level of observed significance achieved at least 10% on the relevant deviance test (Wald test for categorical data or F-test for continuous data). Potential covariates were also explored by reviewing box plots of random effects by covariate group. Two contrasts were considered: gout vs. control and asymptomatic hyperuricaemia vs. control, which were always tested separately. To determine which ultrasound features were associated with a diagnosis of gout or

asymptomatic hyperuricaemia, a stepwise linear regression was undertaken which included tophus presence, double contour sign presence, erosion grade, effusion grade, synovial hypertrophy grade and effusion grade. For the purpose of this analysis, ultrasound features were considered present in each gout and asymptomatic hyperuricaemic participant if present in at least one foot, while for graded variables, the highest grade from both feet was used. All hypothesis tests (excluding covariate testing) were carried out at a 5% level of significance against two-sided alternatives. No adjustment for multiplicity was used, but all test-statistics, their null distributions and their observed significance levels were reported. Data were analysed using IBM SPSS Statistics version 20 and R version 3.2.3.

Sample size calculation

A sample size calculation was undertaken based on adjusted pooling of data derived from studies available at the time of the study conception which had reported the prevalence of the double contour sign at the 1MTPJ in people with gout, asymptomatic hyperuricaemia and/or healthy controls [7, 19, 21, 29, 30]. From these studies the expected prevalence rates of the double contour sign were calculated as 20.6% in gout, 15.4% in asymptomatic hyperuricaemia and 0% in healthy controls. As both 1MTPs in each participant were to be scanned, the required sample size was divided by two and increased by a design effect factor of 1.1 (corresponding to a small intra-class correlation coefficient of approximately 0.1) to account for association in the probability of the double contour sign within a participant. Sample sizes were Familywise Error Rate-adjusted for multiplicity using a Bonferroni correction. The calculated sample sizes were 21 with gout, 29 with asymptomatic hyperuricaemia and 34 healthy controls. These sizes provide approximately 80% power to

detect a difference between asymptomatic hyperuricaemia and controls and 87% power to detect a difference between gout and controls at a Bonferroni-corrected significance level of 5% against two-sided alternatives.

RESULTS

All participants were men with a mean age of 58 years and predominantly of European ethnicity (Table 1). Participants with gout and asymptomatic hyperuricaemia had significantly higher BMI compared to the controls ($p < 0.05$). Participants with gout had a mean (SD) disease duration of 18 (11) years. Eighty-three percent had a history of 1MTPJ acute arthritis and 26% had clinical evidence of 1MTPJ tophi. Six (26%) of participants with gout were crystal-proven, with the remaining (n = 17, 74%) fulfilling the ARA clinical criteria.

Inter-reader reliability was moderate for the presence of the double contour sign, tophi, erosion, synovial hypertrophy and effusion, and good for synovitis (Table 2). The inter-reader reliability for the grading of features was fair to good for erosion, synovial hypertrophy and effusion and excellent for synovitis. Inter-reader reliability for tophus diameter and cartilage thickness was excellent and for erosion diameter was fair to good.

The descriptive statistics for the sonographic features used in the inferential analyses are displayed in Supplementary Table 2. The double contour sign was the most common ultrasound feature of urate deposition and was present in a similar number of 1MTPJs in both gout (n=17, 37%) and asymptomatic hyperuricaemia groups (n=21, 36%). However, only the gout group displayed tophus at the 1MTPJ (n=6, 13%). Synovitis was most common in the gout group (n=20, 44%) compared to the control (n=5, 7%) and asymptomatic

hyperuricaemic groups (n=2, 3%). However, joint effusion was observed more frequently in the asymptomatic hyperuricaemic group (n=13, 22%) compared to the gout group (n=4, 9%). Synovial hypertrophy was less commonly observed and seen in only 2% to 11% of joints. Bone erosion was present in 15 (33%) 1MTPs in the gout group and in only 2 (3%) and 1 (2%) of the control and asymptomatic hyperuricaemic groups, respectively. Cartilage thickness was similar across all groups. Supplementary Tables 3 to 5 show the descriptive statistics for ultrasound features present at each of the dorsal, medial and plantar aspects of the 1MTPJ, respectively. The snowstorm appearance was absent in all participants so was excluded from the inferential analysis.

The distribution of residuals from the linear models for all continuous outcome measures demonstrated sufficient normality to carry out parametric testing. All final models were un-adjusted for covariates which did not achieve significance. The overall presence of ultrasound features at the 1MTP demonstrated significant between-group differences (Table 3). Compared to controls, both participants with gout and with asymptomatic hyperuricaemia had a greater odds of having the double contour sign (OR 3.9; *P*=0.011, OR 3.8; *P*=0.009, respectively). Compared to controls, participants with gout also had an increased odds of having 1MTPJ erosions (OR 10.13; *P*=0.001) and synovitis (OR 9.0; *P*<0.001). Participants with gout also had a non-significant trend towards an increased odds of having 1MTPJ tophus compared to controls (OR 5.08; *P*=0.057). No significant differences were observed for the presence of effusion or synovial hypertrophy between the groups.

Between-group differences were observed for the grading of ultrasound features at the 1MTPJ (Table 4). Compared to controls, participants with gout had a greater odds of having more severe erosions (OR 101.80; *P*<0.001), more severe synovial hypertrophy (OR 11.73;

P=0.002) and more severe synovitis (OR 47.51; *P*=0.002). Compared to controls, participants with asymptomatic hyperuricaemia had a greater odds of having more severe effusion (OR 3.08; *P*=0.046). Compared to controls, participants with gout demonstrated significantly greater tophus diameter (*P*=0.035) and erosion diameter (*P*<0.001) (Table 5).

Using stepwise linear regression analysis, a more severe erosion and synovitis grade and a less severe effusion grade were independently associated with gout compared with asymptomatic hyperuricaemia (model R^2=0.65, *p*<0.001) (Table 6).

DISCUSSION

This study has shown that ultrasound features of urate deposition, soft tissue inflammation and bone damage at the 1MPTJ are present in people with gout despite the absence of clinical symptoms of acute arthritis. In contrast, despite a similar frequency of subclinical urate deposition at the 1MTPJ, individuals with asymptomatic hyperuricemia do not demonstrate features of inflammation or bone erosion on ultrasound. However, they did display a similar frequency of urate deposition at the 1MTPJ.

This study has shown that the double contour sign is significantly more frequent in those with gout. Thirty-seven percent of participants with asymptomatic hyperuricaemia in the current study also demonstrated the double contour sign on ultrasound which is consistent with existing research [18-21] and emphasises the extent of subclinical crystal deposition in individuals with asymptomatic hyperuricaemia.

The frequency of the double contour sign in the patients with gout was similar to those with asymptomatic hyperuricaemia (37% vs. 36%). Although 74% of participants with gout had

clinically-evident tophi and 63% reported recent episodes of acute arthritis, the relatively low frequency of the double contour sign may reflect the use of urate lowering therapy and the mean serum urate level below the treatment target (< 6 mg/dl). Sonographic evidence of urate deposition including both the double contour sign and tophus have been reported to decrease or disappear following urate lowering therapy [31, 32]. This may also explain the lower frequency of tophus (13%) at the 1MTP in our participants with gout compared to previous sonographic investigations which have observed a tophus frequency of 50% to 100% at the 1MTP [7, 10, 30-35].

In the current study, both tophi and bone erosion were noted more frequently at the medial metatarsal head (Supplementary Tables 3 to 5). This erosion pattern is consistent with previous studies in which 46% to 92% of observed 1MTP erosions were located on the medial metatarsal head [7, 36]. This distribution of tophaceous material reflects the strong association between the urate crystal and inflammatory soft tissue components of tophi and the presence of bone erosions [37-39].

Our multiple regression analysis suggests that features other than crystal deposition, specifically synovitis and bone erosion, may be useful in differentiating gout from asymptomatic hyperuricaemia. The greater frequency and increased severity of synovitis in participants with gout (who did not have a gout flare at the time of scanning) suggests that gout is a disease of chronic inflammation with a persistent subclinical immune response to MSU crystals. Individuals with asymptomatic hyperuricaemia, despite demonstrating similar frequency of double contour sign at the 1MTPJ, did not exhibit features of synovitis, indicating that the tissue response to MSU crystals in gout is not present in those with asymptomatic hyperuricaemia. Our data are consistent with recent imaging studies using

both ultrasound and MRI which have reported synovial pannus in 87.5% [40] and synovitis in up to 95.8% of people with intercritical gout [41, 42]. Together, these data suggest that synovial inflammation is a common finding in patients with gout, even in the absence of clinically apparent flares. The relevance of synovial inflammation in predicting future gout flares or joint damage is currently unknown.

Moderate inter-reader reliability was demonstrated in this study for the presence of the double contour sign (ƙ = 0.49) which is in contrast to the majority of previous ultrasound studies which report good to excellent reliability (ƙ = 0.68 to 0.98) [18, 30, 43-47]. There are several factors which may have influenced the reliability of this sign in the current study. Firstly, there is a strong resemblance between the double contour sign and cartilage interface sign, with the latter often appearing as a result of increased reflectivity at a 90° insonation angle, and the former appearing dependant of the insonation angle. Dynamic conformation of the double contour sign could not be performed in the current study as the presence of the sonographic features were assessed from static images. Secondly, the presence of even minimal joint effusion, which was observed frequently in 1MTPJs in the current study, can also accentuate the cartilage interface sign due to enhanced reflectivity [15]. Thin or damaged cartilage, such as that seen in osteoarthritis (which is prevalent at the 1MTPJ) [48], may also impair visualisation of the double contour sign [15]. Importantly, in our analyses, all features were considered present only if both musculoskeletal radiologists reported the feature as present.

The findings from this study should be considered in light of several limitations. Firstly, participants with gout were recruited from secondary-care clinics and had longstanding disease, and it is possible that the findings are not generalizable to people with gout treated

in primary-care. It should also be noted that this study was undertaken prior to publication of the recent 2015 ACR/EULAR classification criteria for gout [14] and the majority of the participants with gout had not undergone microscopic assessment for urate crystals and were classified based on clinical criteria which has limited specificity [49]. Also, the participants with normouricaemia were included based on a single measure of serum urate on the day of the study. Although major diurnal variation in urate is uncommon [50], mild variation in serum urate can occur. It is possible that the single measurement may have misclassified some participants with asymptomatic hyperuricaemia and normouricaemia groups, and that multiple testing of serum urate over a longer time period would have increased the accuracy of this inclusion criterion. Furthermore, participants with asymptomatic hyperuricemia had relatively low hyperuricaemia and it is unclear whether the results would have differed if they had higher urate levels. The cross-sectional nature of study does not allow us to determine the prognostic relevance of asymptomatic ultrasound findings. Future studies may consider the relationship between ultrasound features suggestive of gouty arthritis and clinically-assessed structural and functional characteristics of the 1MTPJ. A longitudinal follow-up to determine the predictive appeal of ultrasound in the development of symptomatic gout in those with asymptomatic hyperuricaemia may also be of value.

In conclusion, this study has shown that compared to normouricaemic controls, ultrasound features of urate deposition, soft tissue inflammation and bone erosion are common at the 1MTPJ in people with gout, despite the absence of clinical symptoms of acute arthritis. Furthermore, although individuals with asymptomatic hyperuricemia lack features of inflammation or structural joint changes on ultrasound, they demonstrate a similar frequency of subclinical urate deposition. Features other than crystal deposition, specifically

synovitis and bone erosion, may be useful in differentiating gout from asymptomatic hyperuricaemia. These data support the concept that gout is a disease of chronic inflammation with a persistent subclinical immune response to the presence of MSU crystals within joints.

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TABLES

Table 1. Demographic characteristics.

Variable	Control	Gout	Asymptomatic hyperuricaemia
N	34	23	29
Gender, male, n (%)	34 (100)	23 (100)	29 (100)
Age, years	58 (14)	58 (14)	58 (19)
Ethnicity, n (%)	European 30 (88) Maori 1 (3) Pacific 0 (0) Asian 3 (9)	European 14 (61) Maori 1 (4) Pacific 4 (17) Asian 4 (17)	European 24 (83) Maori 0 (0) Pacific 3 (10) Asian 2 (7)
BMI, kg/m^2	25.0 (2.9)	30.8 (3.8)†	29.3 (5.9)†
Diuretic use, n (%)	4 (12)	3 (13)	7 (24)
NSAID use, n (%)	7 (21)	14 (61)†	11 (38)
Prednisone use, n (%)	0 (0)	5 (22)	0 (0)
Hypertension, n (%)	9 (26)	16 (70)†	16 (55)†
Cardiovascular disease, n (%)	1 (3)	6 (26)†	5 (17)
Diabetes, n (%)	2 (6)	4 (17)	1 (3)
Serum urate, mg/dl	5.4 (1.0)	5.9 (1.7)	7.7 (0.8)†
Serum urate, mg/dl, range	3.4 – 6.7	4.0 – 10.6	6.9 – 10.6
Highest ever serum urate,	-	10.1 (2.2)	-

mg/dl			
1MTP tenderness, n (%)	1 (3)	6 (26)	1 (3)
1MTP swelling, n (%)	0 (0)	1 (4)	0 (0)
Tender joint count (/68)	0.6 (1.2)	2.6 (6.4)†	1.5 (1.9)
Swollen joint count (/66)	0.0 (0.0)	0.9 (1.2)†	0.2 (0.7)
Crystal-proven gout, n (%)	-	6 (26)	-
Disease duration, years	-	18 (11)	-
Age of onset, years	-	40 (19)	-
Acute flare in preceding 3 months, n (%)	-	15 (63)	-
Number of acute flares in preceding 3 months	-	1.4 (1.4)	-
1MTP flares in preceding 3 months, n (%)	-	6 (26)	-
History of 1MTP flares, n (%)	-	19 (83)	-
Presence of subcutaneous tophi, n (%)	-	17 (74)	-
Presence of 1MTP tophi, n (%)	-	6 (26)	-
Colchicine use, n (%)	-	13 (57)	-
Urate lowering therapy‡, n (%)	-	22 (96)	-
Allopurinol use, n (%)	-	18 (79)	-
Probenecid use, n (%)	-	3 (13)	-
Benzbromarone use, n (%)	-	2 (9)	-

Febuxostat use, n (%)	-	2 (9)	-

Values presented as mean (SD) unless otherwise indicated. [†]Significantly different from control group ($p < 0.05$). [‡]3 patients were taking >1 urate lowering agent. BMI = body mass index; NSAID = non-steroidal anti-inflammatory drugs.

Table 2. Inter-reader reliability of ultrasound features at the 1MTPJ[†]

	N (%)		Percent	k	95% CI for k	
	Reader 1	**Reader 2**	**agreement**		**Lower**	**Upper**
Double contour sign presence	87 (51)	51 (30)	74.4%	0.49	0.37	0.61
Tophus presence	15 (9)	7 (4)	94.2%	0.52	0.26	0.78
Erosion presence	10 (6)	19 (11)	92.4%	0.52	0.29	0.74
Effusion presence	31 (18)	21 (12)	84.9%	0.42	0.23	0.60
Snowstorm presence	2 (1)	0 (0)	98.8%	-	-	-
Synovial hypertrophy presence	15 (9)	14 (8)	93.6%	0.59	0.36	0.81
Synovitis presence	22 (13)	21 (12)	92.4%	0.66	0.48	0.83

	Mean (SD)		$ICC_{3,1}$	95% CI for ICC	
	Reader 1	**Reader 2**		**Lower**	**Upper**
Tophus diameter, mm	0.8 (3.3)	0.5 (3.1)	0.86	0.81	0.89
Erosion grade	0.4 (0.6)	0.4 (0.7)	0.72	0.64	0.79
Erosion diameter, mm	1.2 (2.3)	0.7 (1.7)	0.60	0.50	0.69
Effusion grade	0.8 (0.8)	0.5 (0.7)	0.50	0.38	0.60

Synovial hypertrophy grade	0.6 (0.7)	0.2 (0.7)	0.53	0.41	0.63
Synovitis grade	0.2 (0.5)	0.2 (0.5)	0.81	0.75	0.85
Cartilage thickness, mm[†]	0.64 (0.20)	0.64 (0.19)	0.81	0.75	0.86

[†]n=172 joints. ƙ = kappa statistic; ICC = Intra-class Correlation Coefficient; CI = Confidence Interval.

Table 3. Odds ratios for the presence of ultrasound features at the 1MTPJ

		N (%)	Odds Ratio[†]	95% CI for OR		*p*
				Lower	Upper	
Double Contour Sign	Control	9 (13%)				
	Gout	17 (37%)	3.91	1.37	11.20	**0.011**
	AH	21 (36%)	3.81	1.41	10.36	**0.009**
Tophus	Control	0 (0%)				
	Gout	6 (13%)	5.08	0.96	27.08	0.057
	AH	0 (0%)	1.00	0.12	8.26	1.000
Erosion[‡]	Control	2 (3%)				
	Gout	15 (33%)	10.13	2.75	37.28	**0.001**
	AH	1 (2%)	0.83	0.14	4.88	0.828
Effusion[‡]	Control	12 (18%)				
	Gout	4 (9%)	0.45	0.13	1.61	0.217
	AH	13 (22%)	1.34	0.51	3.54	0.548
Synovial hypertrophy[‡]	Control	0 (0%)				
	Gout	1 (2%)	3.25	0.67	15.73	0.142

	AH	2 (3%)	1.72	0.32	9.13	0.523
	Control	5 (7%)				
Synovitis[‡]	Gout	20 (44%)	9.00	3.10	26.08	**<0.001**
	AH	2 (3%)	0.60	0.14	2.69	0.505

[†]Reference category = control group; All odds ratios are presented unadjusted for covariates. [‡]The overall presence of erosion, effusion and synovial hypertrophy is based on a grade of $\geq$ 2; the overall presence of synovitis is based on a grade of $\geq$ 1. CI = Confidence Interval; OR = Odds Ratio.

Table 4. Odds ratios for grading of ultrasound features at the 1MTPJ

		Odds Ratio[†]	95% CI for OR		*p*
			Lower	Upper	
Erosion grade	Gout	101.80	16.56	625.68	**<0.001**
	AH	1.81	0.49	6.68	0.371
Effusion grade	Gout	0.51	0.15	1.65	0.260
	AH	3.08	1.02	9.31	**0.046**
Synovial hypertrophy grade	Gout	11.73	2.48	55.48	**0.002**
	AH	1.54	0.36	6.52	0.558
Synovitis grade	Gout	47.51	4.29	526.07	**0.002**
	AH	0.46	0.05	4.60	0.511

[†]Reference category = control group. The odds ratio represents the odds of the diagnostic group moving up one grade, compared to the control group moving up one grade. All odds ratios are presented unadjusted for covariates. CI = Confidence Interval; OR = Odds Ratio

Table 5. Linear regression for size and thickness of ultrasound features at the 1MTPJ

		Least-squares mean[†]	Diff.	95% CI for Diff. Lower	95% CI for Diff. Upper	*p*
Tophus diameter, mm	Control	0.00				
	Gout	1.68	1.68	0.12	0.32	**0.035**
	AH	0.00	0.00	-1.46	1.46	1.000
Erosion diameter, mm	Control	0.05				
	Gout	1.55	1.50	0.84	2.16	**<0.001**
	AH	0.05	-0.00	-0.62	0.61	0.989
Cartilage thickness average, mm	Control	0.66				
	Gout	0.64	-0.02	-0.08	0.03	0.364
	AH	0.62	-0.01	-0.06	0.04	0.773

[†]Mean estimates are presented unadjusted for covariates. Diff. = Difference in least-squares mean; CI = Confidence Interval.

Table 6. Stepwise linear regression analysis of ultrasound features independently associated with gout compared with asymptomatic hyperuricaemia

Variables included	**Standardised β**	**Partial R^2 change**	***p***	**Model**	**Variables excluded**
Erosion grade	0.59	0.49	< 0.001	R^2 = 0.65;	Tophus; double
Synovitis grade	0.39	0.16	< 0.001	F = 32.22;	contour sign;
Effusion grade	-0.26	0.07	0.002	P < 0.001	synovial hypertrophy grade.