A Cross Sectional Validation Study of Sonographic Findings of the First Metatarsophalangeal Joint in Gout and Asymptomatic Hyperuricemia

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Abstract

Objective: Musculoskeletal ultrasound has gained recognition in early identification of crystal deposits in the joints and soft tissues. This study aims to validate the sonographic features of 1st metatarsophalangeal joints (MTPJs) in gout and asymptomatic hyperuricemia (AH).

Methods: Patients with gout (n=20) and AH (n=16) underwent a gray-scale ultrasound assessment of both 1st MTPJs on 3 positions (dorsal, medial, plantar) in longitudinal view. The static images were read by 2 blinded trained sonologists for the presence of double contour sign (DCS), erosions, and tophi.

Results: A total of 36 patients (72 1st MTPJs) were included in the study. The overall inter-rater agreement was moderate for detection of DCS on the right (k=0.478, p=0.001) and substantial on the left (k= 0.768, p<0.001). The pooled intra-rater reliabilities of the sonologists yielded perfect agreement for sonologist 2 on detection of DCS and tophi with almost perfect agreement on erosions while reliability of sonologist 1 was statistically significant on detection of DCS on right (k=0.786, p<0.001), with no agreement on erosions and tophi detection (p>0.05).

Conclusion: Among the 3 elemental lesions studied, the greatest inter- and intra-rater reliability were shown in the detection of double contour sign. This study further emphasizes the importance of ultrasound in classifying patients with probable therapeutic options clinicians can offer patients with AH.

Keywords: Double Contour Sign, Gout, Validation Study, Asymptomatic Hyperuricemia

Introduction

Medical non-invasive imaging techniques have revolutionized the recognition of crystal associated arthropathy, most especially gout. Musculoskeletal ultrasound (MSUS) can aid clinicians in establishing the correct diagnosis when polarized microscopic crystal examination is not available. MSUS has gained this notable recognition due to its ability to visualize soft tissue inflammation, joint damage, crystal identification through demonstration of double contour sign (DCS). It is also a relatively inexpensive and accessible evaluation tool that does not expose patients to unnecessary radiation.

The 1st metatarsophalangeal joint (MTPJ) is frequently affected in gout. Therefore, this has gained interest as the primary anatomic site for MSUS evaluation. A study by Stewart et. al. showed the evidence that urate deposits are present at the 1st MTP of individuals with gout and with asymptomatic hyperuricemia (AH); odds ratio (OR) 3.91, p=0.011 and OR 3.81, p=0.009, respectively, compared to normouricemic control participants.[1] In addition, participants with gout had more erosions (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). These observations suggest that the presence of sonographic synovitis and bone erosions at the 1st MTP may help differentiate gout from AH.

In the recent meta-analysis by Lee et. al. consisting of 11 studies including 938 patients with gout and 788 controls, the pooled sensitivity and specificity of US in

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detecting MSU deposits (positive double contour sign) were 65.1% ([95% confidence interval (CI): 62.0–68.2] and 89.0% (96.6–91.1), respectively.[8] The positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were 5.889 (3.365–10.30), 0.359 (0.266–0.485), and 17.61 (11.11–17.92), respectively. When sensitivity and specificity were considered simultaneously, the area under the curve of US was 0.858, indicating a good diagnostic performance.

Earlier studies in 2012 by Peiteado showed that MSUS examination of four joints for two elemental lesions (the double contour sign and hyperechoic cloudy areas) is feasible, reliable and has the face and content validity as a diagnostic test in patients with crystal-proven gout.[2] Bhadu also demonstrated that the knee and the 1st MTPJ might be used to screen for gout.[3] Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive likelihood ratio (LR) of two sites ultrasound findings for gout were 87.2%, 84%, 83.7%, 85.6% and 5.5, respectively.

Currently, no consensus exists on a specific joint to perform ultrasound detection of double contour sign to help confirm crystal deposition. The 1st MTP joint remains the site of interest in different studies on MSUS in gout because this is a very accessible joint. It is therefore critical to evaluate the validity of this site for the clinicians to use this bedside technology as the alternative primary diagnostic technique in place of arthrocentesis and polarizing microscopy studies of synovial fluid for monosodium urate crystal deposition.

General Objective. To validate sonographic features (identification of double contour sign, erosions, tophus) of 1st MTPJs in patients with gouty arthritis and AH

Specific Objective. To determine the inter-rater and intra-rater variability of the of MSUS findings of 1st MTP in gout and AH between two trained musculoskeletal sonologists in a tertiary center

Methodology

This observational cross-sectional study enrolled asymptomatic hyperuricemia and gouty arthritis patients in intercritical asymptomatic period randomly seen and agreed to participate in the study from either the Out-Patient Department or private clinics in the University of Santo Tomas Hospital Section of Rheumatology from September 2019 to March 2020. Study approval was granted by the institution's Research Ethics Committee.

Asymptomatic hyperuricemia (AH) is defined as serum uric acid concentration ≥7.0 mg/dL (360 mmol/L) among adult male and female patients documented in the patients' medical records on at least two occasions within the past two years, never had history of inflammatory mono-, oligo-, or polyarthritis, not on any urate-lowering drug. Secondary causes of hyperuricemia were excluded including malignancy, psoriasis/psoriatic arthritis, chronic hemolytic anemia, myeloproliferative/ lymphoproliferative disorders, Paget's disease, sickle cell anemia, and chronic renal failure, medications used i.e. anti-tuberculous agents (PZA and EMB), cyclosporine A, parathyroid hormone, theophylline, vincristine, diuretics, acetylsalicylic acid (ASA), cyclophosphamide, and current or ongoing use of urate-lowering agents like allopurinol or febuxostat.

Gout patients included male and female adult patients 20-60 years old with diagnosis of gout confirmed by demonstration of MSU crystals written on their medical records at some point during their follow-up care with any Rheumatologist in the hospital. Patients were recruited during their intercritical asymptomatic period of gout, with serum uric acid level at least 7 mg/dl despite being on urate lowering therapy.

Sonographic Machine. The Center uses *Sonosite HFL50*™ with a 6-to15-MHz linear transducer. Both the right and the left 1st MTPJs were scanned by a Rheumatology fellow trained to perform the procedure for this study. The fellow is blinded on the blood uric acid level of the participant. Static grey scale images focused on the dorsal, medial and plantar aspects of each 1st MTPJ in the longitudinal planes were captured. Two sets of best recorded images in the three aspects were sent separately to the two Rheumatology-sonologists blinded to all clinical data of the patients. Interpretation included presence or absence of double contour sign (DCS), erosions, and tophi. The level of agreement between the sonologists on the three sonographic findings was then computed.

Sonographic image interpretation

Double contour sign is defined as 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. *Tophi* is a circumscribed, inhomogeneous, hyperechoic and/or hypoechoic aggregation (that may or may not generate a posterior acoustic shadow), which may be surrounded by a small anechoic rim. *Erosions* are discontinuity of the bone surface, visible in two perpendicular planes.

Statistical Method. The inter-rater and intra-rater reliability using kappa statistics between the two rheumatologist sonologists were determined for the presence of double contour sign, erosion, and tophus on both 1st MTPs.

Results

There were 36 patients included in the study – 20 gout patients and 16 patients with AH. Patients with gout were older than those with AH (*Table I*). The body mass index (BMI) was higher in AH vs gout patients, with a mean of 29.2 kg/m^2 and 23.2 kg/m^2, respectively ($p<0.05$). Patients with AH had higher serum uric acid levels than gout patients ($p<0.05$). The common comorbidities

Table I. Demographic characteristics of participants (N=36)

Variable	Asymptomatic hyperuricemia	Gout
N	16	20
Gender Male Female	 14 2	 9 11
Age in years, Mean ± SD* (Range)	43.6 ± 12 (22-70)	58.7± 15.7 (33-83)
BMI (kg/m^2) Mean ± SD*	29.2 ± 6.5	23.2 ± 4.1
Serum uric acid (mg/dl)	9.4 ± 2.3	8.72 ± 1.7
Family History of gout (%)	3 (19%)	2 (10%)
Co-morbidities		
Hypertension, n (%)	6 (38%)	11 (55%)
Diabetes mellitus, n (%)	2 (13%)	4 (20%)
Dyslipidemia, n (%)	0	0
CKD, n(%)	1 (6%)	0

*Statistically different at *p<0.05*

Table II. Elemental lesions on ultrasonography on all patients as identified by sonologists

	Gout (n = 20)				Asymptomatic hyperuricemia (n= 16)			
	Reader 1		Reader 2		Reader 1		Reader 2	
	Right 1st MTP	Left 1st MTP	Right 1st MTP	Left 1st MTP	Right 1st MTP	Left 1st MTP	Right 1st MTP	Left 1st MTP
DCS	19	15	17	16	16	16	16	15
Erosions	2	4	4	5	4	3	4	5
Tophi	4	3	11	7	6	4	7	7

reported were hypertension and diabetes in both groups.

Table II describes the elemental lesions identified in all participants. Among patients with gout, both sonologists were able to detect DCS on the right 1st MTP in 17 patients and the left 1st MTPs in 15 patients. Erosion was detected in only a patient's right 1st MTP by both sonologists, while two other patients were similarly positive for erosions of their left 1st MTP. Tophi were detected by the sonologists in three patients' right and left 1st MTPs.

Among those with AH, both sonologists identified all 16 participants to be positive for DCS on their right 1st MTP while 15 participants were positive on the left 1st MTP. Erosions were identified similarly on both the right and the left 1st MTP of two patients. Tophi were detected in 43.75% of patients – on the right in four patients and on the left 1st MTPs in three patients.

Reliability analyses. The ƙ values are interpreted as follows: <0 – poor agreement; 0 to 0.2 - slight; 0.21 to 0.4 - fair; 0.4 to 0.6 - moderate; 0.6 to 0.8 - substantial; and 0.8 to 1.0 - almost perfect agreement. Inter-rater reliability is shown in *Table III*.

Double contour sign. There is an overall substantial agreement (*k=0.768*) between the sonologists on detection of double contour sign of the left 1st MTP on all the 36 participants. Both sonologists positively identified DCS on all AH patients, except for left MTP of one patient. There is moderate agreement (*k=0.459, p=0.015*) for both sonologists on the right DCS while outstanding agreement (*k=0.857*) for left DCS in all gout patients.

Erosions. There is a fair agreement (*k = 0.294 to 0.314, p>0.05*) of both sonologists in detecting erosions on all participants. More than half of patients with gout and AH did not have erosions on either 1st MTPs. No agreement was found on detecting erosions in patients with AH (*p>0.05*)

Tophus. There is a moderate agreement (*k=0.421, p<0.05*) between the sonologists in detecting tophi on the left 1st MTPs of all patients, with moderate agreement (*k=0.494, p<0.05*) among patients with gout compared to those with AH. However, both sonologists detected tophus in only three patients with gout (6%). There is no agreement on detecting tophi in patients with AH (*p>0.05*). Intra-rater reliability is shown in *Table IV*

Sonologist 1. There is an overall substantial agreement (*k=0.786, p<0.001*) on DCS of right 1st MTP on all patients. Similarly, a substantial agreement (*k=0.773, p<0.001*) was seen on DCS of right 1st MTP of gout patients while all patients with AH were positive for DCS. On detecting erosions and tophi, there were no agreement on both sets of patients.

Sonologist 2. There is a perfect agreement for Sonologist 2 on detecting DCS, erosion, and tophi on all patients with gout (*p<0.001*). A substantial agreement is seen in detecting erosions on right and left 1st MTP (k=0.6 and 0.673, respectively) among patients with AH. The overall intra-rater reliability on the sonologist is perfect for DCS and tophi and substantial to near perfect on erosions.

Table III. Inter-rater reliability of Two sonologists

	All participants (n=36)			Gout (n=20)			Asymptomatic hyperuricemia (n=16)		
	Kappa	p-values	95% CI	Kappa	p-values	95% CI	Kappa	p-values	95% CI
DCS									
Right	0.478	0.001	-.122,1.077	0.459	0.015	-.139, 1.06	*		
Left	0.768	<0.001	0.46, 1.076	0.857	<0.001	0.587, 1.127	**		
Erosions									
Right	0.294	0.073	-.78, 0.666	0.231	0.264	-.284, 0.746	0.333	0.182	-.188, 0.854
Left	0.314	0.053	0.084, 0.569	0.286	0.197	-.194, 0.766	0.347	0.142	-.147, 0.841
Tophus									
Right	0.222	0.137	-.064, 0.508	0.151	0.369	-.167, 0.469	0.355	0.152	-.106, 0.816
Left	0.421	0.005	0.133, 0.709	0.494	0.010	0.112, 0.876	0.333	0.146	-.104, 0.770

*No statistics computed. All yes answers
**No statistics computed. All yes answers

Table IV. Intra-rater reliability results of Two sonologists

Parameter	Sonologist 1			Sonologist 2		
	Kappa	p-value	99%CI	Kappa	p-value	95%CI
All (n=36)						
DCS						
Right	0.786	<0.001	0.382,1.190	1.0	<0.001	0.9, 1.1
Left	0.036	0.829	-0.313, 0.385	1.0	<0.001	0.9, 1.1
Erosion						
Right	-.180	0.274	-0.165, 0.083	0.75	<0.001	0.487, 1.013
Left	-.108	0.518	-0.412, 0.196	0.84	<0.001	0.626, 1.053
Tophus						
Right	-.167	0.278	-.463, 0.129	1.0	<0.001	0.9, 1.1
Left	0.088	0.592	-.237, 0.413	1.0	<0.001	0.9, 1.1
Gout (n=20)						
DCS						
Right	0.773	<0.001	0.350, 1.196	1.0	<0.001	0.9, 1.1
Left	0.000	1.00	-.433, 0.433	1.0	<0.001	0.9, 1.1
Erosion						
Right	-0.53	0.807	-.459, 0.353	1.0	<0.001	0.9, 1.1
Left	-.125	0.573	-.521, 0.271	1.0	<0.001	0.9, 1.1
Tophus						
Right	-.143	0.436	-.508, 0.221	1.0	<0.001	0.9, 1.1
Left	-.023	0.919	-.455, 0.410	1.0	<0.001	0.9, 1.1
Asymptomatic Hyperuricemia (n=16)						
DCS						
Right	*			*		
Left	-.067	0.790	-.159, 0.025	*		
Erosions						
Right	-.333	0.182	-.551, -0.115	0.600	0.009	0.226, 0.974
Left	-.077	0.755	-.540, 0.386	0.673	0.004	0.273, 1.073
Tophus						
Right	-.161	0.515	-.633, 0.311	1.0	<0.001	0.9, 1.1
Left	0.213	0.377	-.257, 0.683	1.0	<0.001	0.9, 1.1

*No statistics computed because data are constants.

Discussion

Musculoskeletal ultrasound is widely used and considered a validated tool to diagnose early gout through the identification of double contour sign. However, there has been a paucity of publications on its reproducibility. An earlier study published in 2011 in a US Veterans Affairs Hospital observed almost perfect agreement between readers on sonographic findings of monosodium urate crystal deposits.[4] Though the inter-rater reliability of our study is varied, the best agreement found was in detection of DCS which may be considered the basic sonographic finding especially in patients with AH who remains so for prolonged periods.

Morpho-structural changes like tophi were similarly reported in 8% of AH individuals by Pineda et al as well as patellar and Achilles enthesopathies.[9] In a similar cross-sectional study on AH patients by Valea in 2015, 20% had erosions while 30% had tophaceous materials on knee and 1st MTPs performed.[10]

On the point of clinical relevance, although there have been studies on sonographic evidence of monosodium

urate deposits in patients with AH, benefits of starting urate lowering therapies (ULT) to these patients to prevent clinical gout remains undetermined.

Our study is limited by the small sample size and future studies enrolling a greater number of patients can confirm our observations. Another potential limitation is selection bias of participants with gout where only those who have been adherent to their urate lowering agent were involved in the study. Though this was not captured in the data, this could have possibly affected the presence or absence of elemental lesions on ultrasound most especially if hyperuricemia is well controlled.

Conclusion

Among the three elemental lesions studied, the highest inter- and intra-rater reliability was shown in the double contour sign. Further correlation of these findings depends on severity of disease and its duration, as well as joint site.

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Conflict of Interest. None

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