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An ultrasonographic study of gouty arthritis: Synovitis and its relationship to clinical symptoms: A retrospective analysis

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Abstract

Background and Aims: Joint pain is the main symptom of acute attacks in patients with gout, which if not managed properly, can develop into chronic gout. The aim of this study was to investigate the correlation between ultrasound (US) features of gouty arthritis (GA) and its clinical manifestations to provide a basis for diagnosing and evaluating the disease.

Methods: We retrospectively analyzed 182 sites in 139 patients with GA diagnosed by the Rheumatology and Immunology Department. Degree of pain was evaluated using the visual analog scale (VAS). Patients with GA were divided into active and inactive arthritis groups. Statistical differences between the two groups and the correlation between US features and clinical manifestations of the affected joints in patients with GA were analyzed.

Results: The groups had statistical significance in joint effusion, power Doppler ultrasonography (PDS), double contour sign, and bone erosion ($p = 0.02$, 0.001, 0.04, 0.04, respectively). Correlation analysis in this study showed that joint effusion and PDS were positively correlated with degree of pain ($r_s = 0.275$, 0.269; $p < 0.001$, <0.001, respectively). Additionally, PDS was positively correlated with synovitis, joint effusion, bone erosion, and aggregates ($r_s = 0.271$, 0.281, 0.222, 0.281; $p < 0.001$, <0.001, 0.003, <0.001, respectively).

Conclusions: Pathological US features, such as joint effusion, synovitis, PDS and bone erosion were more likely to be detected in GA with clinical signs and symptoms. PDS was positively correlated with joint effusion and synovitis, pain was closely related to PDS and joint effusion, which suggested that the clinical symptoms of GA were related to inflammation, reflecting the patient's condition to some extent. Therefore, musculoskeletal US is a useful clinical tool for managing patients with GA and can provide a reliable reference for diagnosing and treating GA.

KEYWORDS

gouty arthritis, pain, synovitis, ultrasonography

1 | INTRODUCTION

Gouty arthritis (GA), caused by the deposition of monosodium urate (MSU) crystals in and around the joints, is the most common type of inflammatory arthritis in men.[1] The acute phase of the disease has a variety of clinical symptoms, typically the first metatarsophalangeal arthritis, which is usually very painful. This pain is accompanied by symptoms of acute inflammation (redness, fever, swelling, pain, and dysfunction).[2] Pain is the main symptom of acute phase of GA; it is also the most common reason for limiting daily activities. Moreover, if left untreated or poorly managed clinically, it can progress to chronic gout, with local structural and functional changes in the affected joint, including a decrease in muscle strength, restricted joint movement, and increased incidence of musculoskeletal abnormalities.[3] In addition, it significantly impacts the quality of life of the affected population, causing immense psychological and economic burden on patients and their families.[4] Therefore, early diagnosis is essential for timely therapeutic intervention.

Musculoskeletal US has been recognized as an imaging modality for assessing GA because it can reveal soft tissue inflammation, joint injury, and deposition of MSU crystals.[5] US examination is more sensitive than clinical examination and simple radiography for assessing GA.[6] In addition, power Doppler ultrasonography (PDS) enhances the specificity of US[7] and is an easy-to-perform and reliable method for assessing joint synovitis[8,9] and predicting joint injury.[10] Studies of osteoarthritis (OA) of the hand have shown that the causes of symptoms in hand OA remain complex, with US-detected structural changes and inflammation possibly having parts to play.[11] However, whether the US features of the affected joints in GA correlate with the clinical symptoms of joint pain and dysfunction is not known. We aimed to investigate the relationship between musculoskeletal US features and joint pain and dysfunction in patients with GA. In addition, we evaluated the correlation between PDS and other musculoskeletal US features in patients with GA.

2 | METHODS

The data of patients diagnosed with GA in the Department of Nephropathy and Rheumatology of our hospital between 2019 and 2022 were retrospectively analyzed. This study is a retrospective analysis and has no ethical implications.

2.1 | Patients

The inclusion criteria were as follows: (1) patients who complied with the 2015 American Rheumatism Association and the European Union of Resistance Rheumatism joint diagnosis standard of classification of gout, patients presenting with pain, joint swelling, redness, and/or dysfunction were included in the active arthritis group, and those without such symptoms were included in the inactive arthritis group; (2) each patient underwent US examination including power Doppler analysis of the affected joint, and (3) availability of complete clinical data.

The exclusion criteria were as follows: (1) patients with other types of OA, including bacterial arthritis, reactive arthritis, psoriatic arthritis, or spinal arthritis; (2) patients with dementia or other neuropsychiatric diseases who could not cooperate; (3) patients undergoing tumor radiotherapy or chemotherapy, with hematologic diseases, or secondary gout caused by taking certain drugs; (4) patients with a recent fracture or trauma history; (5) presence of GA and rheumatoid arthritis; and (6) incomplete clinical data.

2.2 | Instruments and methods

A Color Doppler US diagnostic instrument (Philips EPIQ 5 ultrasonic diagnostic instrument; Philips Healthcare) was used for US assessment with a probe frequency of 4.0–18.0 MHz. Musculoskeletal US examination conditions were also provided; energy Doppler US was used for low-velocity flow. The color gain was adjusted to the maximum without background noise. All musculoskeletal US examinations were performed by sonographers with professional training in ultrasonography of the musculoskeletal system. The patients' knee, ankle, wrist, elbow, shoulder, interphalangeal, and metatarsophalangeal joints were examined using standard section US in accordance with the standard scanning body position.

The examination time for each patient was not less than 15 min. The instrument was adjusted to enter the musculoskeletal US mode.

2.3 | Ultrasonic characteristics

The US exam was a quantitative synovitis measurement in the largest synovial bursa and semiquantitative grade, as described (Table 1).

Semiquantitative synovitis, bone erosion, joint effusion, and PDS were each evaluated using a 4-grade scale ranging from 0 to 3. Grades 0–1 for bone erosion and synovitis were considered normal, whereas grades 2–3 indicated pathological changes. For PDS and joint effusion, grade 0 was considered normal, whereas grades 1–3 were considered pathological.

2.4 | Pain assessment

The Visual Analogue Scale (VAS) was used to evaluate the degree of clinical pain (0–10 scores). The scores were as follows: comfort, 0–2 scores; mild pain, 3–4 scores; moderate pain, 5–6 scores; severe pain, 7–8 scores; extreme pain, 9–10 scores; the higher the score, the higher the degree of pain.

2.5 | Statistical analysis

Data analysis was done by utilizing IBM SPSS (Statistical Package for Social Sciences) Statistics version 22.0 (IBM). Normality of the data distribution was tested using two independent sample *t* test.

TABLE 1 Semiquantitative grades for synovitis, PDS, bone erosion, and joint effusion.

PDS		Bone erosion	
0	No flow in the synovium	0	Regular bone surface
1	Single vessel signals	1	Bone surface irregularity
2	Confluent vessel signals in less than half of the area evaluated	2	Bone surface defect on 2 planes
3	Vessel signals in more than half of the evaluated area	3	Bone defect with bone destruction
Synovitis		**Joint effusion**	
0	No synovial thickening	0	No joint effusion
1	Minimal synovial thickening of the small joint; 2 mm < synovial thickness of the large joint ≤ 5 mm	1	Minimal effusion of the small joint; 2 mm < effusion depth of the large joint ≤ 5 mm
2	Moderate synovial thickening of the small joint with capsule distension; 5 mm < the synovial thickness of the large joint ≤ 9 mm	2	Moderate effusion of the small joint without joint capsular distension; 5 mm < effusion depth of the large joint ≤ 9 mm
3	Synovial thickening of the small joints with extending to the diaphysis; synovial thickness of the large joint > 9 mm	3	Massive effusion of the small joint with join capsular distension; effusion depth of the large joint > 9 mm

Abbreviation: PDS, power Doppler ultrasonography.

Descriptive statistics such as mean ± standard deviation (for continuous variable) was performed. The categorical variables were measured in percentages and were compared between the groups, using either the χ^2 or Fisher's exact tests. The correlations between variables were evaluated using the Spearman's rank correlation coefficients. A p value of less than 0.05 was considered as a significant level, while $p < 0.01$ was considered significant for correlation analysis (two-tailed).

3 | RESULTS

3.1 | General information of the patients and lesions

The cohort consisted of 139 patients with established GA, for a total of 182 joints. The mean age was >55 years and 87% of the patients were male. The metatarsophalangeal joints (32%) were the most commonly involved joints, followed by the ankle (30%), knee (20%), phalangeal (7.1%), wrist (6.6%), and elbow joints (2.7%) (Figure 1). There was no statistically significant difference in sex, age, or joint site between the two groups ($p > 0.05$).

3.2 | Prevalence of US features

Compared with the nonactive arthritis group, the active arthritis group had a higher rate of joint effusion, PDS, double contour sign (DCS), and bone erosion ($p = 0.02$, 0.001, 0.04, 0.04, respectively), while there was no statistically significant difference in synovitis, aggregates, tophus, and peritendinitis between the two groups ($p = 0.82$, 0.75, 0.22, 0.76, respectively) (Table 2).

3.3 | Correlation analysis

Correlations in this study were interpreted using an r_s value of 0–0.25 to indicate a weak correlation, 0.25–0.5 to indicate a fair correlation, 0.5–0.75 to indicate a moderate correlation, and >0.75 to indicate a strong correlation. Joint effusion and PDS showed positive linear correlations with degree of pain ($r_s = 0.275$, 0.269; $p < 0.001$, <0.001, respectively), indicating a fair correlation. There was, however, no correlation between degree of pain and other ultrasonic characteristics (Table 3).

A statistically significant association was demonstrated between PDS and joint effusion, synovitis, bone erosion, and aggregation ($r_s = 0.281$, 0.271, 0.222, 0.281; $p < 0.001$, <0.001, 0.003, <0.001, respectively). However, there were no statistically significant associations between PDS and other ultrasonic characteristics (Table 3).

4 | DISCUSSIONS

Joint pain during an acute gout attack is caused by inflammation as results of amount of MSU crystals being deposited in the synovial tissue of the surrounding joints. Typical gout attacks often occur at night, with sudden onset and progressive aggravation of pain, reaching a peak at approximately 12 h.[12] The pain is described as tearing, cutting, biting, and unbearable. The affected joints and surrounding soft tissues are usually red and swollen, with increased skin temperature and obvious tenderness. Symptoms resolve spontaneously within more than a few days or 2 weeks. The first attack mostly involves a single joint, and more than 50% of the damage occurs in the first metatarsophalangeal joint. In addition, the ankle, knee, wrist, elbow, and phalangeal joints are also commonly affected. During the transition from acute to chronic gout, tophi may

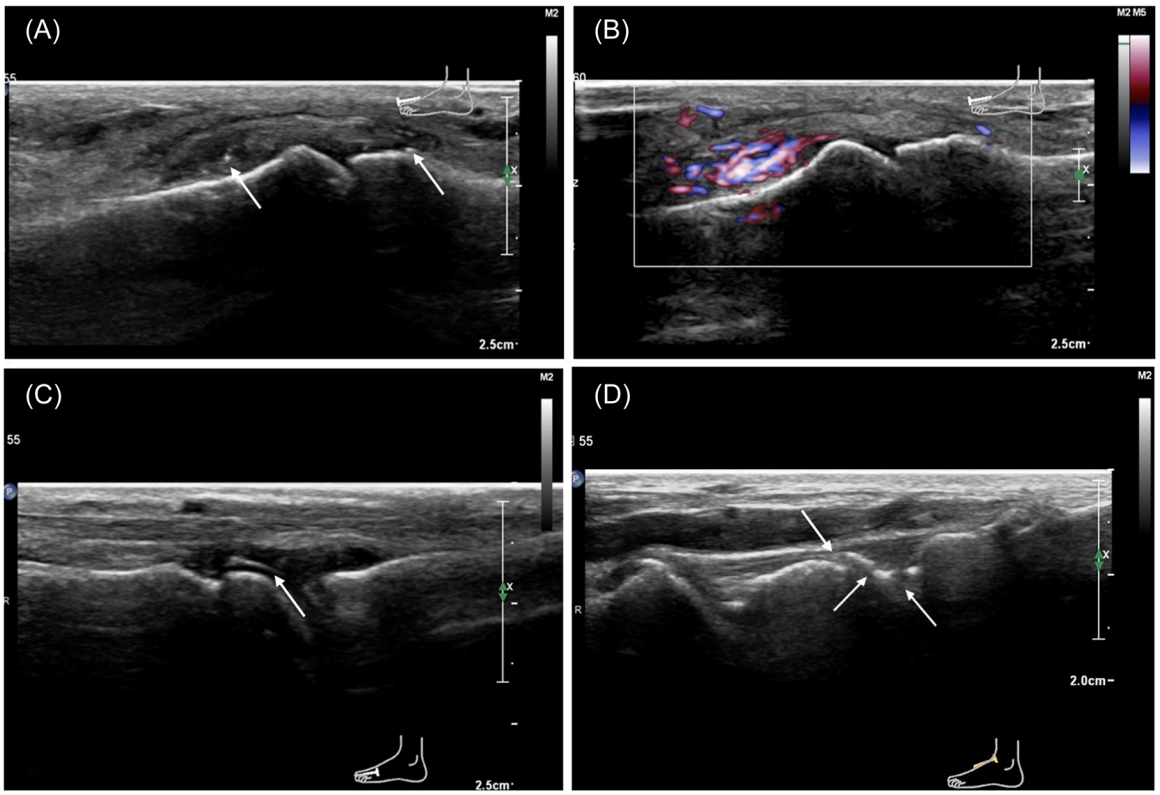

FIGURE 1 (A) Deposition of urate crystals in the first MTP joint of GA. Longitudinal ultrasound image shows synovial hyperplasia, multiple punctate hyperechoic (arrow). (B) Synovitis. Longitudinal ultrasound images of the first MTP joint power Doppler ultrasonography shows abundant blood flow signals (PDS: grade 3). (C) Ultrasound double contour sign. Longitudinal ultrasound image of the second metatarsophalangeal joint shows hyperechoic enhancement (arrow) over the surface of the hyaline cartilage. (D) Bone erosion. Ultrasound appearance of erosion in the talus demonstrates cortical irregularity, focal defect (arrow). GA, gouty arthritis; MTP, metatarsophalangeal; PDS, power Doppler ultrasonography.

or may not be detected on physical examination. Although dual-energy computed tomography can display both MSU crystal deposits and skeletal structures,[13] its high cost limits its use. High-resolution musculoskeletal US exploration can also reveal MSU deposits in the thickened synovium and joint effusion around the affected joint. In addition, it has the advantages of convenience, low cost, and no ionizing radiation, making it more suitable for clinical diagnosis.

The use of PDS-modified gray-scale US in the evaluation of synovitis is widely accepted as a part of all joint ultrasonography. PDS is a sensitive tool for detecting blood flow, especially in small vessels commonly found in the synovium.[14] Even when clinical signs and symptoms of synovitis are absent, ultrasonography can detect subclinical evidence of joint inflammation. In this study, we observed that the incidence of synovitis was high, particularly in symptomatic joints; the clinically active phase of GA showed hypervascularization in the area of synovial hyperplasia and the acute attack was mostly manifested as synovial thickening and PDS. Therefore, an increase in the blood vessels in the synovium of the affected joint could be interpreted as a sign of an inflammatory reaction.

Pain is the main symptom of patients with gout in the acute phase, the main reason for seeking medical attention, and it significantly impacts the quality of life of the affected population. Few studies have investigated the relationship between US features and joint pain in GA. Our study showed that effusion had a positive correlation with degree of pain: in general, higher effusion grading was associated with more pain. Some studies have shown that effusion relates more to mechanical pain than inflammatory pain.[15] Effusion has been shown to affect joint mechanics and muscle activity during gait and can, therefore, be a cause of the mechanical pain.[16] In addition, our study showed that PDS had a positive correlation with degree of pain. PDS in thickened synovium is a sign of US joint inflammation and its association with pain when sitting, and not with walking or stair climbing, suggests that the resting pain during sitting is more likely to be inflammatory pain.[15] Therefore, PDS was an important predictor of joint pain in patients with GA, and also reflected that synovitis was a multifactorial source of joint pain.

Spearman's correlation analysis showed that PDS was positively correlated with synovitis, effusion, and bone erosion. Histological examination of the synovial membrane in acute gout showed lining layer hyperplasia and intense infiltration with neutrophils, mononuclear cells, and lymphocytes.[17,18] Macrophages and a small number of plasma cells were also observed.[18] The synovial lining cell layer can remove debris from the joint cavity and may play a role in controlling the volume and composition of synovial fluid.[19]

TABLE 2 Comparison of the observed indexes between the active arthritis group and the inactive arthritis group.

	Number (n = 182) n (%)	Active arthritis group (n = 134), Mean ± SD n (%)	Inactive arthritis group (n = 48), Mean ± SD n (%)	t/χ^2	p Value
Age		55.28 ± 19.24	56.33 ± 17.42	0.335	0.74[c]
Gender				2.740	0.10[a]
Male	158 (87)	113 (84)	45 (94)		
Female	24 (13)	21 (16)	3 (6)		
Joint site				4.991	0.67[b]
MTP	58 (32)	43 (32)	15 (31)		
Ankle	54 (30)	43 (32)	11 (23)		
Knee	37 (20)	26 (19)	11 (23)		
Wrist	12 (6.6)	7 (5.2)	5 (10)		
Phalangeal	13 (7.1)	10 (7.5)	3 (6.3)		
Elbow	5 (2.7)	3 (2.2)	2 (4.2)		
Shoulder	1 (0.55)	1 (0.75)	0 (0)		
Articulationes intertarseae	2 (1.1)	1 (0.75)	1 (2.1)		
Joint effusion (grade)				10.196	0.02[a]
0		36 (27)	21 (44)		
1		60 (45)	22 (46)		
2		20 (15)	5 (10)		
3		18 (13)	0 (0)		
Synovitis (grade)				1.168	0.82[b]
0		2 (1.5)	0 (0)		
1		17 (13)	6 (13)		
2		36 (27)	10 (21)		
3		79 (59)	32 (67)		
PDS (grade)				16.352	0.001[a]
0		21 (16)	19 (40)		
1		62 (46)	19 (40)		
2		26 (19)	9 (19)		
3		25 (19)	1 (2.1)		
Bone erosion (grade)				8.423	0.04[a]
0		46 (34)	6 (13)		
1		29 (22)	15 (31)		
2		40 (30)	19 (40)		
3		19 (14)	8 (17)		
Aggregation				/	0.75[b]
Without		9 (6.7)	4 (8.3)		
With		125 (93)	44 (92)		
Tophus				1.503	0.22[a]
Without		64 (48)	18 (38)		

(Continues)

TABLE 2 (Continued)

	Number (n = 182) n (%)	Active arthritis group (n = 134), Mean ± SD n (%)	Inactive arthritis group (n = 48), Mean ± SD n (%)	t/χ^2	p Value
With		70 (52)	30 (63)		
DCS				4.300	0.04[a]
Without		40 (30)	7 (15)		
With		94 (70)	41 (85)		
Peritendinitis				0.096	0.76[a]
Without		86 (64)	32 (67)		
With		48 (36)	16 (33)		

Abbreviations: DCS, double contour sign; MTP, metatarsophalangeal; PDS, power Doppler ultrasonography; SD, standard deviation; VAS, visual analog scale.

[a]χ^2 test.

[b]Fisher exact probability method.

[c]Two independent sample t test.

TABLE 3 Correlation analysis between degree of pain and ultrasound features, between PDS and other ultrasound features.

	Degree of pain		PDS	
	r_s	p Value	r_s	p Value
Joint effusion	0.275[a]	<0.001	0.281[a]	<0.001
Synovitis	0.059	0.43	0.271[a]	<0.001
PDS	0.269[a]	<0.001	1.000	/
Bone erosion	−0.126	0.09	0.222[a]	0.003
Tophus	−0.023	0.76	0.118	0.11
Aggregation	0.009	0.91	0.281[a]	<0.001
DCS	−0.032	0.67	0.055	0.46
Peritendinitis	−0.008	0.92	0.130	0.08

Abbreviations: DCS, double contour sign; PDS, power Doppler ultrasonography; r_s, Spearman correlation coefficient.

[a]Spearman's ρ correlation is significant at the 0.01 level (two-tailed).

Light microscopy examination in acute gout showed that numerous capillaries were seen in the synovial membrane,[20] which was associated with erosion development and destruction of adjacent bones.[21,22] This evidence further suggests that the persistence of synovitis, rather than joint pain, is an important factor influencing structural damage in GA and may be a therapeutic target.

Correlation analysis in this study showed that PDS positively correlated with aggregates. For patients with GA, musculoskeletal US can show intra-articular or intra-tendon MSU crystal deposition (DCS, aggregates, and tophi). The distribution of MSU crystals is influenced by joint motion and consequent pressure, which may cause them to move and be deposited into the surrounding soft tissues or large spaces.[23] MSU crystals deposited in the "smaller" upper limb joints are more likely to be "pushed" to the periphery of the joint to aggregate into tophi, and thus they are detected as a hyperechoic aggregate.[24] In contrast, MSU crystal deposition in lower limb joints with "larger" joint cavities may be more likely to be deposited on the cartilage surface; thus, they are detected as a DCS. Katz et al. suggested that MSU crystals may be deposited on the synovium of medium vessels, particularly in the active phase.[25] Cipolletta et al. observed that MSU burden and inflammation detected by US were independent predictors of gout lasting longer than 12 months.[26] In addition, flares should be carefully prevented in patients with a high MSU deposition burden, especially DCS and tophi and inflammation detected by US.

5 | CONCLUSIONS

These results indicate that GA patients with clinical signs and symptoms of active arthritis, were more likely to have detectable pathological US features, such as joint effusion, synovitis, PDS, and bone erosion than in patients with inactive arthritis. In addition, correlation analysis showed that PDS was positively correlated with joint effusion and synovitis, and the degree of pain was positively correlated with joint effusion and PDS, indicating that the higher is the grade of PDS, the higher the grade of synovitis and joint effusion, and the more obvious is the degree of pain. This evidence further suggests that clinical manifestations of acute attack of GA may be related to inflammation, reflecting the patient's condition to some extent and providing important reference information for the diagnosis and treatment, and also enhancing the confidence of clinicians in the management of GA patients. Therefore, musculoskeletal US can be used as a suitable tool for the management of GA patients, and is worth popularizing.

6 | LIMITATIONS

This study had some limitations. First, although all sonographers were trained in musculoskeletal US, the level of experience was uneven, and the reliability of sonographers was not calibrated and evaluated,

which could have led to bias. Second, it was not possible to enroll patients with no joint pain in the painless arthritis group, and it was difficult to obtain individuals with persistent pain states (present or absent) during the development of GA. Third, this was a single-center, cross-sectional, study with a limited number of patients. In addition, this was a retrospective analysis, and the data were collected from the results of previous examinations. It is impossible to prevent sonographers from asking patients for clinical information, so there was a certain bias in the selection of study patients. Therefore, the research conclusions need to be further verified by a double-blind study with a larger sample size.

AUTHOR CONTRIBUTIONS

Wenli Zheng: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; supervision; validation; visualization; writing—original draft; writing—review and editing. **Peiming Lu**: Conceptualization; supervision. **Dianhu Jiang**: Conceptualization; supervision. **Lixian Chen**: Conceptualization; data curation; formal analysis; methodology. **Yi Li**: Conceptualization; data curation; investigation; methodology. **Haowen Deng**: Conceptualization; data curation; investigation; methodology.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. All authors have read and approved the final version of the manuscript, corresponding author had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

The lead author Wenli Zheng affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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