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SHORT REPORT

Dynamic assessment of the double contour sign by ultrasonography helps to distinguish between gout and calcium pyrophosphate deposition disease

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ABSTRACT

Objective To test whether the double contour (DC) sign has a different dynamic behaviour in gout and calcium pyrophosphate deposition (CPPD) and whether the dynamic assessment of the DC sign increases its accuracy in gout diagnosis.

Methods This cross-sectional analysis included patients with gout meeting the 2015 ACR/EULAR classification criteria and patients with crystal-proven diagnosis of CPPD. Hyaline cartilages were explored by ultrasound (US) to detect the DC sign (ie, abnormal hyperechoic band over the superficial margin of hyaline cartilages) and its dynamic behaviour during joint movement was evaluated ((ie, movement of the DC sign together with subchondral bone (DC sign), or in the opposite direction (pseudo DC sign)).

Results Eighty-one patients with gout and 84 patients with CPPD underwent US assessment. Among them, 47 patients with gout and 9 patients with CPPD had evidence of the DC sign. During dynamic assessment, in all 47/47 patients with gout there was a DC sign. Conversely, in 7/9 (77.8%) patients with CPPD, there was a pseudo DC sign ($p<0.01$).

The presence of DC sign during static assessment had a sensitivity, specificity and accuracy of 58.0% (95% CI 46.5% to 68.9%), 89.3% (95% CI 80.6% to 95.0%) and 73.9% (95% CI 66.5% to 80.5%) for gout, respectively. The dynamic evaluation improved the DC sign's diagnostic performance ($p=0.01$) as the specificity (97.6% (95% CI 91.7% to 99.7%)) and the accuracy (78.2% (95% CI 71.1% to 84.2%)) increased without loss in sensitivity.

Conclusion The dynamic US assessment of the DC sign may help to differentiate the DC sign due to MSU crystals from the pseudo DC sign seen in CPPD, as they move in opposite directions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The double contour (DC) sign is a ultrasound (US) sign highly specific for gout. However, some studies have reported its presence in patients with calcium pyrophosphate deposition (CPPD) disease thereby questioning its specificity.

⇒ A previous case report describes pseudo DC sign (ie, deposition of CPP crystals in capsules and/or ligaments moving in the opposite direction to the underlying hyaline cartilage and subcortical bone during dynamic examination) in a cadaver with diffuse CPPD.

WHAT THIS STUDY ADDS

⇒ The DC sign in gout and CPPD has different dynamic behaviour. In gout the superficial margin moves together with the subchondral bone (DC sign), whereas in CPPD it moves in the opposite direction (pseudo DC sign).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Dynamic assessment of the DC sign may improve the ability of US in differentiating gout and CPPD disease.

INTRODUCTION

Ultrasound (US) has been increasingly used for the diagnosis of gout. Three main US findings have been described in gout: aggregates, double contour (DC) sign and tophi.[1] In 2015, the Outcome Measure in Rheumatology (OMERACT) US working group developed consensus-based definitions for these findings and found acceptable reliability and high levels of specificity and positive predictive value (PPV).[1] The pooled specificity and PPV of the DC sign was 0.87 (95% CI 0.80 to 0.92) and 0.87 (95% CI 0.84 to 0.90), in a recent meta-analysis.[2] For these reasons, the DC sign has been incorporated in the 2015 ACR/EULAR classification criteria for gout.[3]

Nevertheless, some studies have questioned the specificity of the DC sign for gout as it has been reported in calcium pyrophosphate deposition (CPPD),[4–6] with a prevalence ranging from 7.1%[6] to 20.2%.[5] A previous case report has demonstrated that the deposition of CPP crystals in capsules and/or ligaments appearing to be located on top of the hyaline cartilage generates a pseudo DC sign in CPPD disease. The dynamic behaviour of the pseudo DC sign appears to be different from that of the DC sign as the hyperechoic band moves in the opposite direction to the underlying subchondral bone.[7] This makes it important to evaluate whether the DC sign seen in gout and CPPD disease has different behaviour during dynamic assessment in real-life clinical setting.

Therefore, the aim of the present study was to test whether the DC sign has a different dynamic behaviour in gout and CPPD disease and whether the US dynamic assessment of the DC sign increases its accuracy in the diagnosis of gout.

METHODS

Study design and patients

A cross-sectional analysis of data from consecutive patients acquired during two prospective cohort studies[8 9] and a cross-sectional case–control study[10] between September 2019 and June 2022 was carried out at the Polytechnic University of Marche (Ancona, Italy). Data collection and study's hypothesis were planned before the index test and reference standard were performed.

Patients with gout meeting the 2015 ACR/EULAR classification criteria and patients with a crystal-proven diagnosis of CPPD were consecutively recruited from among those participating in three US imaging studies.[8–10] These criteria were selected as the current and internationally recognised criteria for classifying patients as having gout or CPPD disease. Patients with mixed crystal arthritis were excluded from all studies.

Since reference[10] refers to a study whose enrolment phase ended in November 2022, online supplemental material S1 contains the study's protocol and online supplemental table S1 contains the demographic and clinical data of the population included in the present study.

The Standards for Reporting of Diagnostic Accuracy (STARD) checklist was used to draft the manuscript.

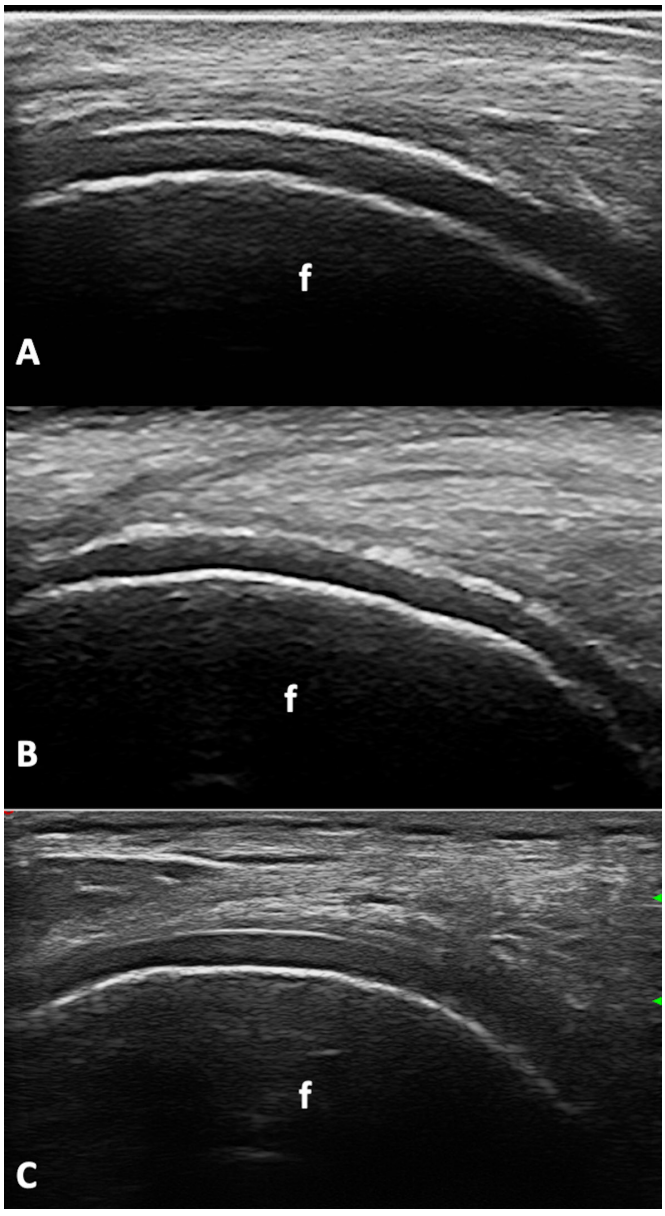

Figure 1 US findings fulfilling the OMERACT definition for DC sign in gout (A) and CPPD disease (B).Panel C shows the normal US appearance of the hyaline cartilage. Dorsal longitudinal scans of the femoral condyles' hyaline cartilage acquired with the knee in full flexion. CPPD, calcium pyrophosphate deposition; DC, double contour sign; f, femur; OMERACT, Outcome Measures in Rheumatology; US, ultrasound.

US assessment

Patients underwent baseline US examination using standardised scanning protocols as reported in online supplemental table S2.

US assessments were carried out according to the 2017 EULAR standardised procedures for US imaging in rheumatology[11] by a rheumatologist blinded to patients' diagnosis.[8–10]

The hyaline cartilage of the scanned joints was explored to detect US findings indicative of crystal deposits (ie, DC sign and CPP deposits within the cartilage layer),[1 12] paying particular attention to differentiate the DC sign from the cartilage interface sign, which is visible only when the outer margin of the hyaline cartilage is perpendicularly insonated by the US beam and usually is thinner than the DC sign and the bony cortex (figure 1). Furthermore, once a DC sign was identified, its dynamic behaviour during joint movement was evaluated while holding the probe steady (ie, movement of the DC sign together with the hyaline cartilage and the subchondral bone, indicating crystals attached on the cartilage surface or in the opposite direction, indicating crystals in the joint capsule

or ligaments) (online supplemental video S1 and online supplemental video S2). The cartilage interface sign has a dynamic behaviour similar to the DC sign seen in gout (online supplemental video S3).

The US examinations were conducted using either a MyLab Class C (Esaote, Italy) equipped with a linear probe operating at 6–18 MHz and a convex probe operating at 2–7 MHz, or a Logiq 9 (GE, USA) equipped with 2–8 MHz and 8–15 MHz linear probes.

Joints revealing synovial effusion during US evaluation were excluded from the analysis as the presence of synovial effusion may generate an image mimicking the DC sign.[13]

Statistical analysis

The χ^2 test was used to compare categorical variables, whereas quantitative variables were compared using Student's t test or Mann-Whitney U test depending on their distribution, as appropriate.

The performance of the DC sign in discriminating between gout and CPPD disease was reported using sensitivity, specificity and accuracy. The diagnostic accuracy of the static and the dynamic assessment of the DC sign was evaluated by comparing the area under the receiver operating characteristic curves (AUROCs).

Patients with missing data and indeterminate reference standard results were excluded from the analyses.

The following sensitivity analyses were carried out to test the validity of our findings:

- Including only patients with a crystal-proven diagnosis of either gout or CPPD disease.
- Excluding patients with CPPD disease and the DC sign coexisting with CPP deposits within the hyaline cartilage of the same joint.
- Excluding patients with CPPD disease and the DC sign coexisting with any CPP deposits in the same joint.

The level of significance was set at <0.05. Data were analysed using Stata V.14.

RESULTS

Eighty-one patients with gout and 84 patients with CPPD disease underwent US assessment. Among them, 47 (58.0%) patients with gout and 9 (10.7%) with CPPD disease had a static US image indicating a DC sign in one or more joints (57 joints in gout and 13 joints in CPPD disease patients). Patients' demographic, clinical and US data are reported in table 1. No patients with relevant missing data were excluded from the analyses.

The DC sign moved together with the hyaline cartilage during the dynamic assessment in all 57 joints of the patients with gout showing US evidence of the DC sign. On the other hand, in 10 (76.9%) out of 13 joints of the patients with CPPD disease showing US evidence of the DC sign, it moved in the opposite direction to the hyaline cartilage during the dynamic evaluation (ie, a pseudo DC sign was present) (p<0.01). When data were considered at patient level, the DC sign moved together with the hyaline cartilage during dynamic evaluation in all 47 patients with gout, whereas in 7 (77.8%) of 9 patients with CPPD disease, the DC sign moved in the opposite direction (ie, a pseudo DC sign was present) to the hyaline cartilage during the dynamic assessment (p<0.01).

The static assessment of the DC sign had a sensitivity, specificity and accuracy of 58.0% (95% CI 46.5% to 68.9%), 89.3% (95% CI 80.6% to 95.0%) and 73.9% (95% CI 66.5% to 80.5%) for gout in this cohort of people with gout and CPPD disease. Including the dynamic assessment of the DC sign significantly increased the performance of US in the diagnosis of gout (AUROC of the DC sign's static assessment: 0.74, 95% CI 0.67 to 0.80; AUROC of the DC sign's dynamic assessment: 0.78, 95% CI 0.72 to 0.83, p=0.01). Indeed, the specificity (97.6% (95% CI 91.7% to 99.7%)) and the accuracy (78.2% (95% CI 71.1% to 84.2%)) increased with no loss in sensitivity. The sensitivity analyses confirmed the results of the main analysis (table 2).

DISCUSSION

The results of the present study can be summarised as follows: first, the DC sign is identified in up to 10% of patients with CPPD disease. Second, in the majority of patients with CPPD disease, the pseudo DC sign has a dynamic behaviour different from the gout DC sign. Third, the dynamic assessment of the DC sign improves the ability of US to diagnose gout compared with the presence of a DC sign in static images alone.

Pathological studies have highlighted that crystals deposited in different tissues are responsible for the DC and pseudo DC sign in gout and CPPD disease, respectively. As shown recently by Filippou *et al*, the deposition of CPP crystals in capsules and/or ligaments and located just above the hyaline cartilage generates the pseudo DC sign in CPPD disease.[7] On the contrary, monosodium urate (MSU) crystals lie directly on the chondral surface and generates the DC sign in gout.[14] Such anatomical difference accounts for the different behaviour of the pseudo DC in CPPD disease and the DC sign in gout.

In 2 (2.4%) out of 84 patients with CPPD disease, the DC sign was indistinguishable from the gout DC sign in both static and dynamic assessment. Some explanations could account for this observation. First, such patients diagnosed with CPPD disease could actually have an undiagnosed mixed crystal arthritis. Second, this may be related to a peculiar localisation of intracartilaginous CPP crystals on the edge of the hyaline cartilage rather than in its middle layer or the 'shedding' of the CPP crystals into the joint space and their subsequent deposition on the cartilage surface.[15] For these reasons, US may not be able to discriminate all patients with gout and CPPD disease based on the DC sign only. Consequently, synovial fluid aspiration and analysis should be performed whenever possible when crystal arthritis is suspected.

Table 1 Demographic, clinical and US data of patients with gout and CPPD disease with US evidence of DC sign

	Patients with gout (n=47)	Patients with CPPD disease (n=9)
Age (years, mean (SD))	59.9 (14.8)	71.8 (7.4)
Sex, female (n (%))	3 (6.4%)	5 (55.6%)
Body mass index (kg/m^2, mean (SD))	25.9 (4.8)	25.0 (2.3)
Familiar history of gout (n (%))	11 (23.4%)	NA
Disease duration since diagnosis (years, mean (SD))	6.3 (7.1)	6.5 (3.9)
Subcutaneous tophi (n (%))	5 (10.6%)	0
Urate-lowering therapy (n (%))	47 (100%)	0
C reactive protein level (mg/dL, mean (SD))	0.6 (0.4)	0.5 (0.7)
Serum urate, latest measurement (µmol/l, mean (SD))	342.9 (94.9)	NA
Latest measurement of serum urate >360 µmol/L(n (%))	30 (37.0%)	NA
Crystal-proven diagnosis	30 (63.8%)	9 (100%)
EULAR clinical presentation		
- Osteoarthritis with CPPD (n, (%))	NA	5 (55.6%)
- Acute CPP crystal arthritis(n, (%))	NA	2 (22.2%)
- Chronic inflammatory CPP crystal arthritis(n, (%))	NA	2 (22.2%)
CPPD disease aetiology		
- Idiopathic (n, %)	NA	7 (77.8%)
- Associated with predisposing conditions (n, %)	NA	2 (22.2%)
US evidence of the OMERACT DC sign (no of joints)	57	13
- DC sign with CPP deposits within the HC	0	4 (30.8%)
- DC sign without CPP deposits within the HC in the same joint	57 (100%)	9 (69.2%)
- DC sign without any CPP deposits in the same joint	55 (96.5%)	3 (23.1%)
Dynamic behaviour of the OMERACT DC sign (no of joints)		
- Moving together with the HC	57 (100%)	3 (23.1%)
- Moving in the opposite direction to the HC	0	10 (76.9%)
Distribution of joints with US evidence of the OMERACT DC sign		
- Knee	20 (35.1%)	6 (46.2%)
- Ankle	14 (24.6%)	1 (7.7%)
- MTP1j	17 (29.8%)	NA
- Elbow	NA	3 (23.1%)
- Wrist	1 (1.8%)	0
- MCP2j	5 (8.8%)	3 (23.1%)

CPPD, calcium pyrophosphate deposition; DC, double contour; HC, hyaline cartilage; MCP2j, metacarpophalangeal joint of the second digit; MTP1j, metatarsophalangeal joint of the first digit; NA, not assessed; OMERACT, Outcome Measure in Rheumatology; US, ultrasound.

The present study has also some limitations. First, a single sonographer performed all US examinations in a single centre, thus limiting the generalisability of our results. However, the sonographer was blinded to clinical and laboratory data. The use of baseline data from different US studies is unlikely to reduce the validity of our findings. Nevertheless, our observations need to be confirmed in an independent cohort of patients with crystal arthritis diagnosed using the very same reference standard, enrolled using the same inclusion/exclusion criteria and imaged by different sonographers performing the same scanning protocol.

Second, patients with mixed crystal arthritis were excluded impairing any definite conclusions on the role of the DC sign in such a condition. However, it would be difficult to study such patients as it would be impossible to attribute the DC sign to each of the different crystal types present without histological examination. Third, the low sample size was a study's limitation, as only 10% of patients with CPPD disease had US evidence of the DC sign. Fourth, the pseudo DC sign was found at knees, elbows and metacarpophalangeal joints. Therefore, the dynamic behaviour of the DC sign in other joints of patients with CPPD disease needs to be further

Table 2 Diagnostic accuracy of the OMERACT DC sign for gout with and without dynamic assessment

	Patients with gout	Patients with CPPD	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)
DC sign, static assessment*	47 (58.0%)	9 (10.7%)	58.0% (95% CI 46.5% to 68.9%)	89.3% (95% CI 80.6% to 95.0%)	73.9% (95% CI 66.5% to 80.5%)
DC sign, static assessment in patients with crystal-proven diagnosis†	30 (50.8%)	9 (10.7%)	50.8% (95% CI 37.5% to 64.1%)	89.3% (95% CI 80.6% to 95.0%)	73.4% (95% CI 65.4% to 80.5%)
DC sign, static assessment excluding those with the coexistence of the DC sign and CPP deposits within the hyaline cartilage‡	47 (58.0%)	5 (6.3%)	58.0% (95% CI 46.5% to 68.9%)	93.8% (95% CI 86.0% to 97.9%)	75.8% (95% CI 62.9% to 74.1%)
DC sign, static assessment excluding those with the coexistence of the DC sign and any CPP deposits in the same joint§	45 (57.0%)	3 (3.8%)	57.0% (95% CI 45.3% to 68.1%)	96.2% (95% CI 89.2% to 99.2%)	76.4% (95% CI 69.0% to 82.8%)
DC sign, dynamic assessment	47 (58.0%)	2 (2.4%)	58.0% (95% CI 46.5% to 68.9%)	97.6% (95% CI 91.7% to 99.7%)	78.2% (95% CI 71.1% to 84.2%)
DC sign, dynamic assessment in patients with crystal-proven diagnosis†	30 (50.8%)	2 (2.4%)	50.8% (95% CI 37.5% to 64.1%)	97.6% (95% CI 91.7% to 99.7%)	78.3% (95% CI 70.7% to 84.8%)
DC sign, dynamic assessment excluding those with the coexistence of the DC sign and CPP deposits within the hyaline cartilage‡	47 (58.0%)	1 (1.3%)	58.0% (95% CI 46.5% to 68.9%)	98.8% (95% CI 93.2% to 99.9%)	78.3% (95% CI 71.1% to 84.4%)
DC sign, dynamic assessment excluding those with the coexistence of the DC sign and any CPP deposits in the same joint§	45 (57.0%)	0	57.0% (95% CI 45.3% to 68.1%)	100% (95% CI 95.4% to 100%)	78.3% (95% CI 71.1% to 84.5%)

*Eighty-one patients with gout and 84 patients with CPPD disease were included in the analysis.
†Fifty-nine patients with gout and 84 patients with CPPD disease were included in the analysis.
‡Eighty-one patients with gout and 80 patients with CPPD disease were included in the analysis.
§Seventy-nine patients with gout and 78 patients with CPPD disease were included in the analysis.
CPPD, calcium pyrophosphate deposition; DC, double contour; OMERACT, Outcome Measure in Rheumatology.

investigated. Fifth, the lack of a comparative imaging technique such as DECT represented another limitation of the study. Finally, we excluded patients with joint effusion from the analyses. Although this last limitation should not represent a major bias, as the distinction between the hyaline cartilage's interface sign and the DC sign is usually easy, the validity of our findings in these patients with joint effusion needs to be tested.

CONCLUSION

The dynamic assessment of the DC sign may help US to differentiate the DC sign due to MSU crystals from the pseudo DC sign seen in CPPD disease, as they move in opposite directions.

Contributors AA contributed to the study design and interpretation of the results, supervised the analysis and critically reviewed the paper. ADM contributed to the study design, advised on the interpretation of the results and critically reviewed the paper. EC conceived the idea for the study, contributed to the study design, reviewed the literature, performed the analysis and wrote the draft of the manuscript. EF conceived the idea for the study, contributed to the study design, advised on the interpretation of the results and critically reviewed the paper. WG contributed to the study design, advised on the interpretation of the results and critically reviewed the paper. All authors have approved the submitted version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Patient consent for publication Not applicable.

Ethics approval The studies were approved by the local Ethics Committee (CERM 168/2019 and 345/2021). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The authors confirm that the data supporting the findings of this study are available within the article and its online supplemental materials.

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