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BRIEF REPORT

Knee effusion: ultrasound as a useful tool for the detection of calcium pyrophosphate crystals

Santiago Ruta[1] · **Erika Catay**[1] · **Josefina Marin**[1] · **Javier Rosa**[1] · **Ricardo García-Monaco**[2] · **Enrique R. Soriano**[1,3]

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Abstract The objective of this study was to evaluate the sensitivity and specificity of ultrasound (US) and conventional radiography (CR) for the detection of calcium pyrophosphate (CPP) crystals in patients with knee effusion. Consecutive patients ≥50 years old with knee effusion were included. All patients underwent arthrocentesis with aspiration of synovial fluid (SF) and subsequent analysis of CPP crystals using plain light and polarizing light microscopy. US and CR of the involved knee were performed immediately after arthrocentesis. CR results were read by an experienced rheumatologist, searching for chondrocalcinosis. US examinations were carried out by an experienced rheumatologist blinded to all clinical and imaging data. The following US abnormal findings were considered indicative of CPP crystals deposition (CPPD): (1) hyperechoic bands within the femoral hyaline cartilage layer, and (2) hyperechoic sparkling spots in meniscal fibrocartilage. A total of 75 knees were evaluated in the same number of patients. Analysis of SF revealed CPP crystals in 15 out of 75 (20 %) knees: all (10) patients with previous diagnosis of CPPD, 3 patients with previous diagnosis of primary knee osteoarthritis (OA) and 2 patients without previous definitive diagnosis of a rheumatic condition. Using SF analysis as reference method, sensitivity and specificity for US findings was 60 and 96.7 %, respectively, while CR showed a sensitivity of 40 % and a specificity of 83.3 %. US results showed high specificity with acceptable sensitivity to detect CPP crystals in patients with knee effusion. Compared with CR, US results had better specificity and sensitivity. US may be used in daily rheumatologic practice when CPPD is suspected.

Keywords Crystal arthropathies · Imaging · Radiology · Ultrasound

✉ Santiago Ruta
santiago.ruta@hospitalitaliano.org.ar

Erika Catay
erika.catay@hospitalitaliano.org.ar

Josefina Marin
josefina.marin@hospitalitaliano.org.ar

Javier Rosa
javier.rosa@hospitalitaliano.org.ar

Ricardo García-Monaco
ricardo.garciamonaco@hospitalitaliano.org.ar

Enrique R. Soriano
enrique.soriano@hospitalitaliano.org.ar

[1] Rheumatology Unit, Internal Medicine Department, Hospital Italiano de Buenos Aires, and University Institute Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

[2] Radiology Department, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

[3] Fundacion Dr. Pedro M. Catoggio para el Progreso de la Reumatología, Buenos Aires, Argentina

Introduction

Calcium pyrophosphate (CPP) crystals deposition (CPPD), that occurs almost exclusively in articular tissues, most commonly fibrocartilage and hyaline cartilage, is an important cause of arthritis, mainly in elderly people [1–4]. Prevalence of CPPD varies from 7 to 10 % in people over 60 years and shows equal sex distribution [5]. Definitive diagnosis of CPPD is based on identification of characteristic CPP crystals on synovial fluid (SF), or occasionally biopsied tissue, and a routine search for these crystals is recommended in all SF

samples obtained from undiagnosed inflamed joints, especially from knees or wrists of older patients [6].

Conventional radiography (CR) is usually the first imaging method used by most physicians, including rheumatologists, to determine the presence of chondrocalcinosis. However, its detection in proven cases of CPP crystal arthritis varies widely depending on the population and joint examined and its sensitivity and specificity remains unknown [6].

Ultrasound (US) has become as an important tool in the assessment of patients with rheumatic conditions. The high reflectivity of the crystalline aggregates and the possibility of detecting minimal deposits account for the use of US in revealing crystals [7]. Although a number of papers have described the potential of US to detect abnormal findings usually seen in CPPD [8–12], few studies were designed to evaluate the diagnostic test properties of US in crystals related arthropathies [13–15].

The knees are one of the most affected joints in patients with CPPD [1, 6, 16]. Knee monoarthritis is relatively common and usually needs SF aspiration, mainly to exclude infections and to confirm the diagnosis of crystal disease. We designed the present study to evaluate the ability of US and CR to detect CPP crystals in patients with knee effusion.

Materials and methods

Consecutive patients older than 50 years with knee effusion on clinical examination, seen at the outpatient rheumatology unit, who underwent arthrocentesis and subsequent SF analysis for the detection of crystals, were included. Patients with a history of trauma and/or steroid injections within the last 6 weeks were excluded. In all patients, both US and CR of the involved knee were performed immediately after SF aspiration.

The study was conducted according to the Declaration of Helsinki and local regulations. Ethical approval for the study was obtained from the Hospital local Ethics Committee and informed consent was obtained from all patients.

Synovial fluid was analyzed by an expert biologist, blinded to both clinical and imaging data, using plain light and polarizing light microscopy, within 6 h of aspiration. Crystals with a parallelepipedic or rhomboid shape and weak birefringence with positive elongation were considered to be CPP crystals [6].

Comparative anteroposterior radiography of the knees with the patient in a standing position were performed in all patients and were read by an experienced rheumatologist (JR) blinded to all clinical and US data, searching for chondrocalcinosis.

US examinations were performed by another experienced rheumatologist (SR) in this imaging technique, who was blinded to all clinical and CR data. A MyLab 70 XV (Esaote Biomedica, Genoa, Italy) machine equipped with a broadband 4–13 MHz linear probe was used. US scanning technique were performed according to standard methods [17], including suprapatellar views (transverse and longitudinal) with the knee in maximal possible flexion to assess femoral hyaline cartilage and lateral and medial longitudinal views with the knee extended (as possible) to evaluate lateral and medial meniscal fibrocartilage, respectively. The following US abnormal findings were considered indicative of CPPD [6]: (1) hyperechoic bands within the femoral hyaline cartilage layer, and (2) hyperechoic sparkling spots in meniscal fibrocartilage (Figure 1).

Statistical analysis

Quantitative variables were expressed as means and standard deviation (SD). Categorical variables were expressed as percentages (%). Sensitivity, specificity, positive and negative predictive values, and accuracy for the detection of CPP were calculated with their 95 % confidence interval (CI) using SF results as the reference method. The area under receiver operating characteristic (ROC) curve was calculated.

Results

A total of 75 knees were evaluated in the same number of patients. Fifty-two (69.3 %) were female and mean age (SD) was 67.5 years (15.8). Twenty-four (32 %) patients had a previous diagnosis of primary knee osteoarthritis (OA), 15 (20 %) rheumatoid arthritis (RA), 10 (13.3 %) CPPD (McCarty criteria), 8 (10.7 %) psoriatic arthritis (PsA), 5 (6.7 %) systemic lupus erytematosus and 13 (17.3 %) patients

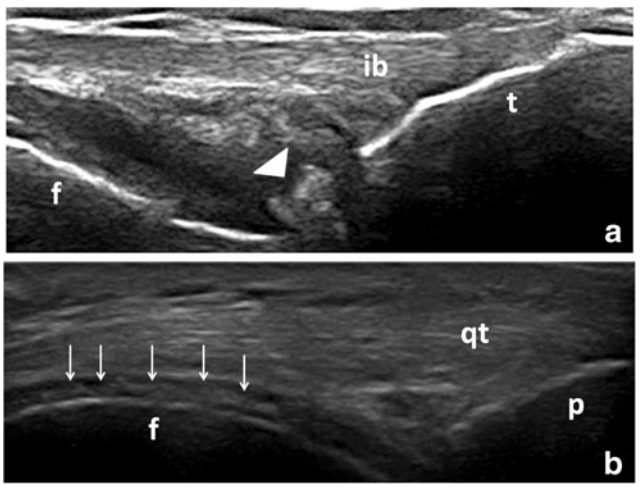

Fig. 1 Representative ultrasound images. Knee. **a**. Lateral longitudinal scan. Hyperechoic sparkling spots in lateral meniscal fibrocartilage (*arrowhead*). **b**. Suprapatellar longitudinal scan with knee in maximal flexion. Hyperechoic bands within the femoral hyaline cartilage layer (*arrows*). *f* femur, *t* tibia, *ib* iliotibial band, *p* patella, *qt* quadriceps tendon

had knee effusion without definitive diagnosis. Analysis of SF revealed CPP crystals in 15 out of 75 (20 %) examined knees: all (10) patients with previous diagnosis of CPPD, 3 patients with previous diagnosis of primary knee OA and 2 patients without previous definitive diagnosis of a rheumatic condition.

US detected signs indicative of CPP crystals in 11 out of 75 (14.7 %) knees. Hyperechoic bands within the femoral hyaline cartilage layer were found in 8/11 (72.7 %) and hyperechoic sparkling spots in meniscal fibrocartilage were detected in 10/11 (90.9 %) knees. Among 11 knees with CPP crystals detected by US, only one showed hyperechoic bands within the femoral hyaline cartilage layer without meniscal fibrocartilage involvement.

CR revealed chondrocalcinosis in 16 out of 75 (21.3 %) knees

Among 15 knees with CPP crystals on SF examination, in 9 (60 %) and 6 (40 %) knees CPP crystals were also detected by US and CR, respectively. US demonstrated CPP crystals in 2 knees with negative SF, while CR showed chondrocalcinosis in 10 knees with SF negative for CPP crystals. Using SF analysis as reference method, sensitivity and specificity for US findings was 60 % and 96.7 %, respectively, while CR showed a sensitivity of 40 % and a specificity of 83.7 % (Table 1).

The area under receiver operating characteristic (ROC) curve was 0.783 (95 % CI: 0.653–0.913) and 0.616 (95 % CI: 0.479–0.753) for US findings indicative of CPP crystals and for chondrocalcinosis by CR, respectively (Figure 2).

Neither SF analysis nor US examinations showed monosodium urate crystals or findings indicative of urate deposition.

Discussion

In the latest recommendations for the diagnosis and management of gout and CPPD crystal deposition disease, the diagnostic potential of advanced imaging techniques, including ultrasound, has been recognized [6, 18, 19]. This is, however, supported by few studies [19]. A Medline search using the keywords 'ultrasound', and 'calcium pyrophosphate deposition disease' revealed that there are only 20 studies focused on ultrasound in diagnosing and/or monitoring CPPD crystal deposition disease [19]. Over the last 2 years, only 14 studies, carried out in patients with gout and/or CPPD crystal deposition disease, enrolled more than 20 patients [19].

In the present study, the presence of CPP crystals on SF analysis was used as a reference method to determine the diagnostic test properties of US and CR in the detection of

Table 1 Ultrasound and conventional radiology diagnostic test properties for the detection of CPP crystals using synovial fluid analysis as the reference method

		Synovial fluid analysis: CPP crystals		Sensitivity, % (95 % CI)	Specificity, % (95 % CI)	Positive predictive value, % (95 % CI)	Negative predictive value, % (95 % CI)	Accuracy, % (95 % CI)
		Negative	Positive					
Ultrasound: hyperechoic bands within the femoral hyaline cartilage layer *or* hyperechoic sparkling spots in meniscal fibrocartilage	Negative	58	6	60 (35.7-80.2)	96.7 (88.6-99.1)	81.8 (52.3-94.8)	90.6 (81–95.6)	89.3 (80.3-94.5)
	Positive	2	9					
Ultrasound: hyperechoic bands within the femoral hyaline cartilage layer	Negative	60	7	53.3 (30.1-75.2)	100 (94–100)	100 (67.6-100)	89.6(80–94.8)	90.7 (82–95.4)
	Positive	0	8					
Ultrasound: hyperechoic sparkling spots in meniscal fibrocartilage	Negative	58	7	53.3 (30.1-75.2)	96.7 (88.6-99.1)	80 (49–94.3)	89.2 (79.4-94.7)	88 (78.7-93.6)
	Positive	2	8					
Conventional radiology: chondrocalcinosis	Negative	50	9	40 (19.8-64.3)	83.3 (72–90.7)	37.5 (18.5-61.4)	84.7 (73.5-91.8)	74.7 (63.8-83.1)
	Positive	10	6					

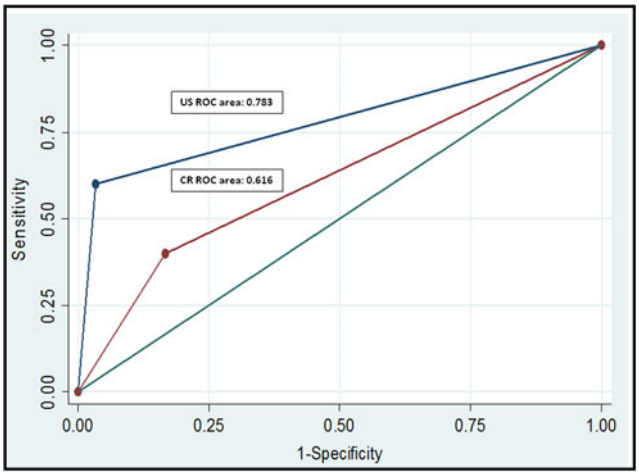

Fig. 2 Comparative receiver operating characteristic (ROC) curves for ultrasound (US ROC area) and radiology (CR ROC area) for the detection of CPP crystals, using synovial fluid analysis as a reference method

pathological findings indicative of CPPD in patients with knee effusion.

US showed a high specificity with acceptable sensitivity to detect CPP crystals in patients older than 50 years with knee effusion. Related to specificity, our results are in agreement with previous reports: 96.4 % by Filippou G, et al. [14] , 97.6 % by Filippucci E, et al. [13], 100 % by Ellabban AS, et al. [20], and 92.3 % by Ottaviani S, et al. [21], supporting these data. It should be noted that our study was performed in a rheumatology outpatient clinic including patients with knee effusion, regardless of the previous diagnosis (without excluding patients with other rheumatic diseases). Although the sensitivity in our study was acceptable, it was lower than previously reported [13, 14, 21, 22], with a range between 68.7 to 100 %. This could be explained in part by the fact that different populations were included, and a different gold standard was used for the diagnosis of CPPD in the different studies. In our study we included patients with previous rheumatic conditions that could reduce the ability of US to detect CPP crystals, as might be the presence of osteophytes in patients with primary knee OA, and thickness reduction of the hyaline cartilage layer in OA, RA and PsA. A lower sensitivity could also be explained by technical reasons, as some patients with knee effusion were unable to achieve the maximal degree of knee flexion necessary to obtain maximal exposure of the femoral cartilage surface.

To date, specificity and sensitivity of chondrocalcinosis in plain knee radiographs for the diagnosis of CPP crystals is not well established. Our study showed a good specificity, but lower than the 100 % recently reported by both Ellabban A, et al. [20] and Ottaviani S, et al. [21] and a low sensitivity. This result was similar to the one reported by Barskova BG, et al. [22] (52 %), lower than reported by Ottaviani S, et al. [21] (60 %) and higher than reported by Ellabban A, et al. [20] (13.2 %). Among patients with a previous diagnosis of CPPD according to the McCarty criteria, SF analysis revealed the presence of CPP crystals in all of them, US in nine (60 %), and CR in six (40 %). Among the others, five patients without previous diagnosis of CPPD, in whom CPP crystals were found on SF analysis, neither US nor CR showed CPP crystals. Three of these patients had knee OA and both joint space narrowing and the presence of osteophytes could reduce the ability of these imaging methods to detect CPP crystals [19, 20]. It is possible that crystal detection by SF analysis and US is more dependent on crystal amounts than CR. This would bias specificity towards US if SF is used as a gold standard. Although this might explain the higher sensitivity of US in our study, this concept is not supported by other studies were CR had a low sensitivity even when large amounts of crystals were found in the synovial fluid [21].

The present study has some limitations. Although SF analysis is considered the reference method and was used as a gold standard to evaluate the diagnostic test properties of CR and US, CPP crystals cannot always be detected in SF mainly due to both its size and the possibility to vary its presence on the time. As was described in the previous paragraphs, some patients with knee effusion could not achieve the maximum degree of knee flexion necessary to obtain the maximum exposure of the femoral cartilage surface for US examination, which might decrease the ability of US to detect CPP crystals into the cartilage layer. Another limitation is the fact that we did not evaluate both intra-observer and inter-observer reliability about radiological and US findings. Another limitation is the small number of patients with positive CPP crystals in SF analysis, which can introduce some uncertainties about the real values of the diagnostic performance of CR and US, as reflected by a wide confidence interval in some of the performance measurements.

Ultrasound has many practical advantages over other imaging techniques in assessing microcrystal arthropathies, including: noninvasive and quick examination of multiple anatomic areas, safe and reliable guide to aspirate fluid collections, and good sensitivity and specificity as shown in our study [19].

In conclusion, US showed high specificity and acceptable sensitivity for the diagnosis of CPPD in patients older than 50 years with knee effusion. This is an imaging method that is innocuous, patient-friendly, and can be performed during a rheumatology assessment as an extension of the clinical examination could become one of the first diagnostic methods in patients with knee effusion in whom CPPD arthropathy is suspected.

Compliance with Ethical Standards The study was conducted according to the Declaration of Helsinki and local regulations. Ethical approval for the study was obtained from the Hospital local Ethics Committee and informed consent was obtained from all patients.

Disclosures None

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