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Detection of Subclinical Crystal Arthropathy in Primary Knee Osteoarthritis Patients

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ABSTRACT

Background: Crystal deposition is one of the most common arthropathies among the elderly. Similarly, osteoarthritis (OA) considers the most common joint pathology amongst the elderly; it is usually associated with significant pain, disability, and even synovitis.

Objective: The aim of the work was to detect Crystals in Non-symptomatized crystal arthropathy in cases of primary knee Osteoarthritis.

Patients and Methods: 50 patients with primary knee osteoarthritis who diagnosed according to the American College of Rheumatology classification criteria for osteoarthritis. Patients underwent to history taking, clinical examination, laboratory examination, knee US, plain radiography and synovial fluid analysis.

Results: Fifty patients (35 females, 15 males) were enrolled. Mean values were 65.4 years ± 13.5 SD for age and 50.7 months ± 35.5 SD for disease duration. Plain radiography revealed chondrocalcinosis in 4 patients (8%). Crystals were detected by US in 36 knees (72%), 24 patients had calcification characteristic of CPPD and 12 patients had calcifications characteristic of MSU crystals deposition. synovial fluid examination revealed crystal deposition in 38 knees (76%), it was MSU in 12 patients and CPPD in 26 patients. The sensitivity of US for the detection of calcification was (83.3%) while that of plain X-ray was (22.2%), and the specificity was (93.8%) and (90.2%) respectively. There is statistically significant difference between patients with crystal deposition and patients without crystal deposition as regard WOMAC stiffness score.

Conclusion: Subclinical crystals were detected in a significant number of Primary Knee Osteoarthritis Patients. US showed high specificity and acceptable sensitivity for the diagnosis of Crystal Arthropathy.

Keywords: Subclinical Crystal Arthropathy, Knee Osteoarthritis.

INTRODUCTION

Osteoarthritis (OA) is a chronic degenerative synovial joints disease that usually affects elderly people. The exact causes of (OA) are still unclear and there is much controversy in the literature as to the specific sequence of events that provoke the onset of the heterogeneous disease we know as OA [(1)]. In spite of being a degenerative process, an inflammatory component of variable intensity had been reported significantly [(2)].

Calcium pyrophosphate crystal deposition (CPPD) associates with ageing, osteoarthritis (OA), uncommon metabolic diseases, mutations and polymorphisms in the ankylosis human gene (ANKH). CPPD is frequently polyarticular, occurs due to a generalized articular predisposition, and the association between CPPD and OA is joint specific, for example, CPPD associates with knee OA, but not with hip OA. Other recently identified associations include knee malalignment (knee CC), low cortical BMD and soft tissue calcification. CPPD is generally asymptomatic. A recent study reported that knees with OA plus CC at the index joint, or at distant joints (in absence of index joint CC), were more likely to have attrition. CPPD can cause acute CPP crystal arthritis, chronic CPP crystal inflammatory arthritis, and is frequently present in joints with OA [(3)].

The interpretation of such findings, the underlying pathogenic theories, and their contribution to the existence/severity of the inflammatory degenerative process in OA awaits in-depth understanding and evidence-based clarifications. A number of explanations have been postulated. Most commonly accepted is the one about infammasomes and crystals [(4)].

MSU and CPP crystals can directly stimulate the innate inflammatory cells like macrophages promoting infammasomes activation leading to the subsequent downstream production and secretion of active inflammatory cytokines such as IL-18 and IL-1β, a finding that strongly correlated with OA severity [(5, 6)].

Intraarticular calcific crystal deposits frequently go underdiagnosed, being largely dependent on physician's knowledge and judgment, compounded by the lack of reproducibility of plain radiography in CDD, another shortcoming of radiographic diagnosis. Diverse reports revealed a high discordance between clinical criteria of pain, stiffness, and functional disability and radiographic changes in knee OA [(7)].

While magnetic resonance imaging stood out as an accurate yet an expensive and time-consuming alternative [(8)]. Joint aspiration and polarized microscopic examination are considered the gold standard measure for diagnosis of crystal arthropathies.

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Although not a difficult procedure, the use of joint aspiration on a routine basis remains limited, being a relatively invasive procedure that requires sufficient training, practice, and patient acceptance, particularly in the absence of significant effusion. Such a challenge to perfect practice and diagnosis emphasized the need for an alternative approach to achieve diagnosis of intraarticular crystal deposits aimed at improving standards of care, particularly in OA with an inflammatory element [(9)]. With the recent inclusion of ultrasound (US) as a bedside radio-imaging modality in the diagnosis of articular and periarticular pathologies, rheumatologists are experiencing a paradigm shift that has effectively improved daily practice towards an earlier diagnosis, decision-making, and follow-up of a particular pathology [(10)].

The aim of study was to detect Crystals in Non-symptomatized crystal arthropathy in cases of primary knee joint Osteoarthritis.

PATIENTS AND METHODS

This study included a total of 50 patients with primary knee osteoarthritis who diagnosed as primary osteoarthritis according to the American College of Rheumatology classification criteria for osteoarthritis [(11)]. Patients were selected from those attending the Outpatient Clinic, Rheumatology & Rehabilitation Department, Al-Azhar University Hospital, Assuit, in the period from September 2019 to April 2020. Verbal and written consent were obtained from all participates in the study.

***Ethical Consideration*:**

This study was ethically approved by Ethical Committee of Faculty of Medicine Al-Azhar University, Assuit.

Exclusion criteria: Secondary osteoarthritis, autoimmune connective tissue diseases, diabetes mellitus, parathyroid disorders, thyroid disorders, clinically manifested crystal arthropahies, malignancies and blood diseases.

All patients were subjected to:

1- Full History taking including: (i) Personal History. **(ii) History of present illness:** with analysis of the following complaints of joint symptoms: pain, stiffness, functional limitation, pain severity and functional limitation. Extra articular symptoms. **(iii) Past History:** of chronic diseases, Medication, Surgical, Allergy, Blood transfusion. **(iv) Family History:** similar conditions, Rheumatic illness.

2- Clinical Examination including: (i) General examination: General condition, vital signs. **(ii) Locomotor examination including** combined inspection and palpation of all joints for swelling, tenderness, warmth and limitation of range of motion.

3- Investigations:

(A) Laboratory: Complete Blood count (CBC), ESR, CRP, Rheumatoid Factor, serum uric acid, TSH, fasting and 2hr post prandial glucose and PTH.

(B) Radiology: (i) Plain x-ray on both knees. (ii) Ultrasonographic examination of the knee joint: US scanning technique adopting the standard scans for the assessment of knee cartilage described in the EULAR guidelines for musculoskeletal ultrasound in rheumatology. **(iii) Synovial Fluid Analysis:** Using polarized light microscopy ZIESS Lab.A1 AXIO for the identification of crystals.

Wet smear analysis by polarized microscopy:

For crystal examination, a drop of the synovial fluid may be placed directly in a microscope slide and attenuated with a coverslip. If the fluid is placed in a tube for later examination, heparin must be used as the anticoagulant. The color changes from blue to yellow or vice versa. Crystals that are yellow when oriented parallel to the axis of the compensator are -Ve birefringent, whereas crystals that are blue are +Ve birefringent [(12)].

Statistical analysis

Data were coded, entered and analyzed by the statistical Package for the Social Sciences (SPSS for windows version 20). Number and percent was calculated for categorical variables, mean and standard division was calculated for continuous variables. Chi-square test used to compare qualitative variables. Two-tailed tests were used throughout and statistical significance was set at the conventional level of less than 0.05.

RESULTS

Table (1): Description of demographic data of all studied patients.

		Studied patients (N = 50)	
Age (years)	**Mean ±SD**	65.4 ± 13.5	
	Min - Max	50 – 80	
Sex	**Male**	15	30%
	Female	35	70%
Disease duration (months)	**Mean ±SD**	50.7 ± 35.5	
	Min - Max	10 – 240	
BMI (kg/m^2)	**Mean ±SD**	33.1 ± 6.3	
	Min - Max	24.2 – 53.3	

As regard age, the mean age of all studied patients was 65.4 ± 13.5 years with minimum age of 50 years and maximum age of 80 years. As regard sex, there were 15 males (30%) and 35 females (70%) in the studied patients. As regard duration of disease, the mean duration of all studied patients was 50.7 ± 35.5 months with minimum duration

of 10 months and maximum duration of 240 months. As regard BMI, the mean BMI of all studied patients was 33.1 ± 6.3 kg/m^2 with minimum BMI of 24.2 kg/m^2 and maximum BMI of 53.3 kg/m^2.

Table (2): Description of X-Ray examination of all studied patients.

		Studied patients (N = 50)	
X-Ray examination (Chondrocalcinosis)	**Present**	4	8%
	Not present	46	92%

This table shows the description of X-Ray examination of all studied patients. Chondrocalcinosis was present in 4 patients (8%) and not present in 46 patients (92%) of all studied patients.

Table (3): Description of MSUS examination of all studied patients.

		Studied patients (N = 50)	
Effusion	**Not present**	0	0%
	Present	50	100%
Total crystal deposition	**No**	14	28%
	Yes	36	72%
Site of deposition (n = 36)	**Hyaline cartilage**	18	50%
	Fibro-cartilage	16	44.4%
	Recesses & bursa	2	5.6%
Pattern of calcification	**Double contour sign MSU**	12	33.3%
	Calcific deposits of CPPD	24	66.7%
Pattern of CPPD (n = 24)	**Pattern I**	6	25%
	Pattern II	16	66.7%
	Pattern III	2	8.3%

As regard effusion, it was present in all studied patients (100%). As regard total crystal deposition, it was present in 36 patients (72%) and not present in 14 patients (28%) of all studied patients. As regard site of deposition, it was in hyaline cartilage in 18 patients (50%), it was in fibro-cartilage in 16 patients (44.4%) and in recesses & bursa in 2 patients (5.6%). As regard pattern of calcification, it was double contour sign MUS in 12 patients (33.3%) and calcific deposits of CPPD in 24 patients (66.7%). As regard pattern of CPPD, it was pattern I in 6 patients (25%), pattern II in 16 patients (66.7%) and pattern III in 2 patients (8.3%).

Table (4): Description of synovial fluid examination of all studied patients.

		Studied patients (N = 50)	
Total crystal deposition	**No**	12	24%
	Yes	38	76%
Type of crystal (n = 38)	**MSU**	12	31.6%
	CPPD	26	68.4%

As regard total crystal deposition, it was present in 38 patients (76%) and not present in 12 patients (24%) of all studied patients. As regard type of crystal, it was MUS in 12 patients (31.6%) and CPPD in 26 patients (68.4%).

Table (5): Diagnostic performance of U/S and X-Ray in relation to synovial fluid results.

(n = 50)	**True positive**		**True negative**		**False positive**		**False negative**	
U/S	**15**	**30%**	**30**	**60%**	**2**	**4%**	**3**	**6%**
X-Ray	**2**	**4%**	**37**	**74%**	**4**	**8%**	**7**	**14%**
	Sensitivity		**Specificity**		**PPV**		**NPV**	**Accuracy**
U/S	**83.3%**		**93.8%**		**88.2%**		**90.9%**	**90%**
X-Ray	**22.2%**		**90.2%**		**33.3%**		**84.1%**	**78%**

The diagnostic performance of U/S in relation to synovial fluid results. Total studied patients were 50 patients. There were 15 patients (30%) true positive, 30 patients (60%) true negative, 2 patients (4%) false positive and 3 patients (6%) false negative. Thus U/S had the sensitivity of 83.3%, specificity of 93.8%, PPV of 88.2%, NPV of 90.9% and accuracy of 90%. The diagnostic performance of X-Ray in relation to synovial fluid results. Total studied patients were 50 patients. There were 2 patients (4%) true positive, 37 patients (74%) true negative, 4 patients (8%) false positive and 7 patients (14%) false negative. Thus X-Ray had the sensitivity of 22.2%, specificity of 90.2%, PPV of 33.3%, NPV of 84.1% and accuracy of 78%.

Table (6): Comparisons of WOMAC score as regard Crystal deposition in studied patients

			Crystal deposition		Stat. test	P-value
			Yes (n = 36)	No (n = 14)		
WOMAC Score	**Pain**	**Mean ±SD**	14.1±2.3	13.9±1.9	T = 0.28	0.774 NS
	Stiffness	**Mean ±SD**	5.9±1.8	4.2±1.1	**T = 3.3**	**0.002 S**
	Disability	**Mean ±SD**	48.1±13.2	46.2±8.5	T = 0.49	0.620 NS

T: independent sample T test. **S:** p-value < 0.05 is considered significant.
NS: p-value > 0.05 is considered non-significant.

Table (6) shows no statistically significant differences between patients with crystal deposition and patients without crystal deposition as regard pain and disability score (p-value > 0.05). It shows also statistically significant difference between patients with crystal deposition and patients without crystal deposition as regard stiffness score (p-value < 0.05).

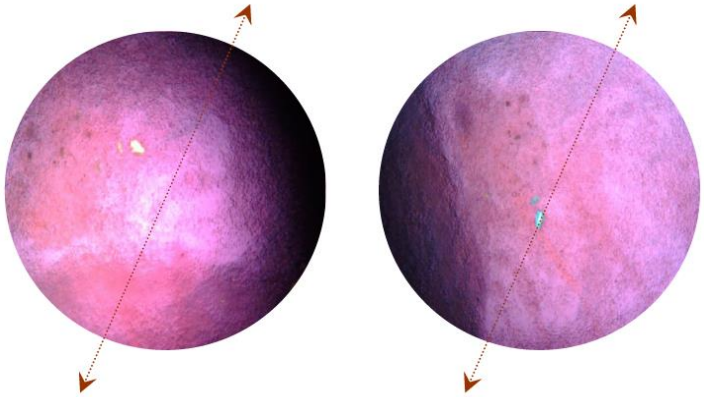

Fig. (1): CPPD Crystal in Synovial Fluid Examined by Polarized Microscopy
Rhomboid-shaped +Ve birefringent crystal (blue when oriented parallel to the axis of the compensator).

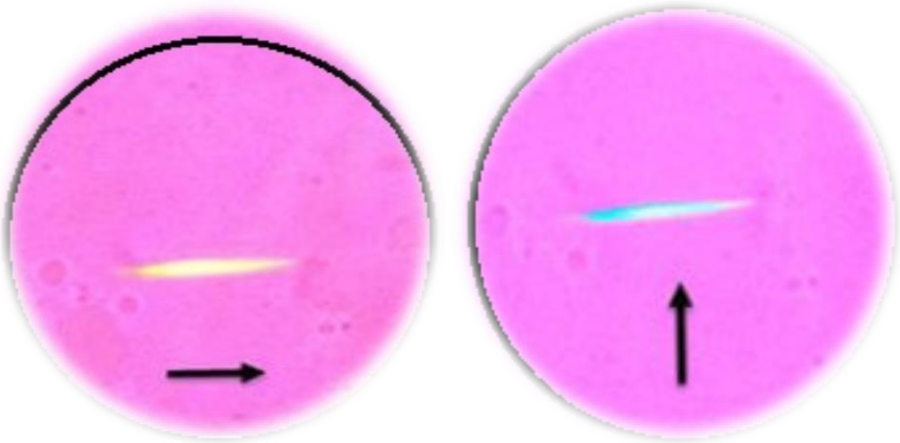

Fig. (2): MSU Crystal in Synovial Fluid Examined by Polarized Microscopy
Needle-like shaped and strong -Ve birefringence of MSU-crystal under polarized microscopy.

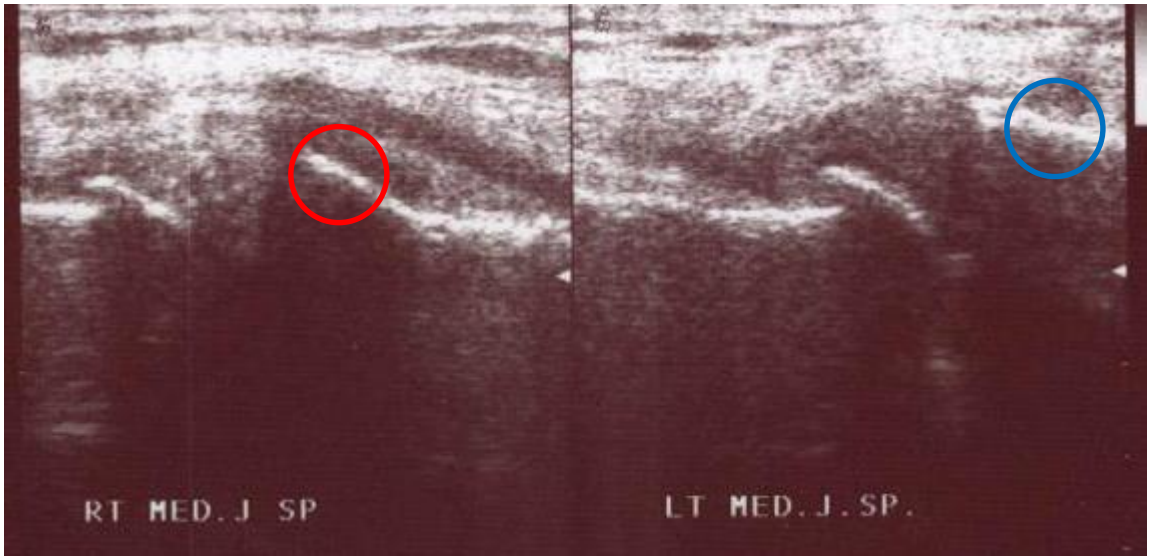

Fig. (3): The view of MSUS longitudinal section (L.S.) image shows several thin hyperechoic spots in fibrocartilage of right medial meniscus or punctate pattern (Pattern II) in right knee joint (the red circle) while left medial meniscus appears normal (the blue circle).

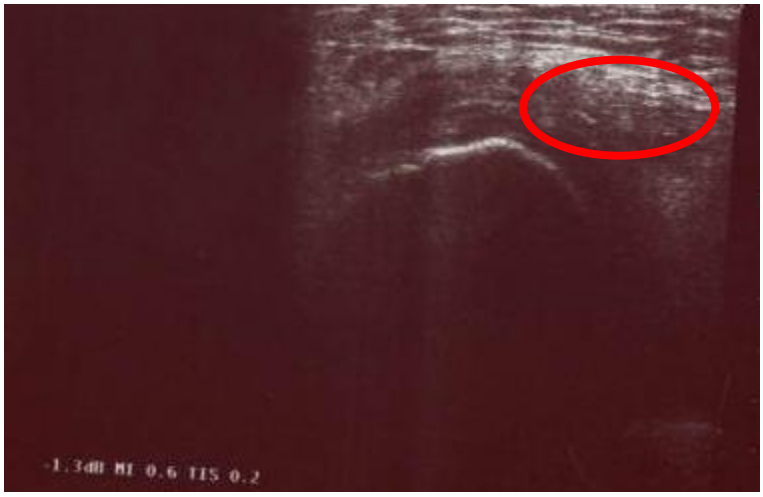

Fig. (4): The view of MSUS longitudinal section (L.S.) image shows thin hyperechoic band in articular cartilage which reflects linear calcification (Pattern I) in knee joint.

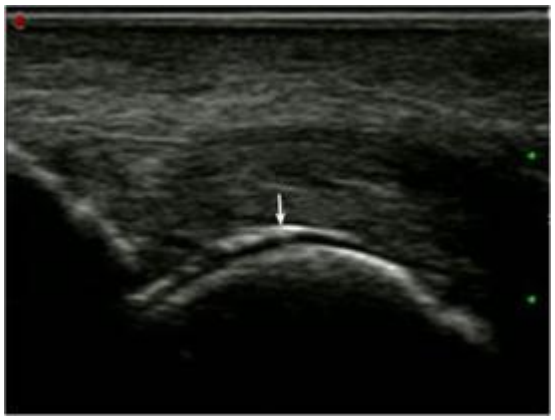

Fig. (5): An anterior transverse scan of the left knee joint in full and 30-degree flexion using a linear probe illustrating a Double contour sign, which is a characteristic sign of MSU deposit.

DISCUSSION

In the current study, US scanning using the OMERACT definitions and scanning technique **Filippou *et al.*** [13] could successfully detect calcifications in the hyaline cartilage, fibrocartilage, recesses, and bursa in 50%, 44.5%, and 5.5% of the scanned knees, respectively.

The aim of the current work was to investigate the prevalence of subclinical crystal deposition in knee OA and evaluate the sensitivity and specificity of ultrasound (US) and plain radiography for the detection of crystals in patients with Primary Knee OA.

The study additionally investigated the impact of sonographically detected crystal deposits on stiffness, pain, and functional disability as practically recognized functional indicators of the existing inflammatory degenerative process in knee OA.

The scanning rheumatologist had been blinded to plain radiography and serum uric acid levels. Crystal deposits were sonographically detected in 36 (72%) of our patients, while conventional radiography could detect Crystals in 4 (8%) patients only. Analysis of SF revealed crystals in 38 (76%).

In the current study, all patients with sonographic or conventional radiographic calcifications, had crystals in their synovial fluids, and no patient without crystals in the synovial fluid analysis had either radiographic or sonographic finding of calcifications.

In the current study, we found that the US pattern of calcification of CPPD deposits in the knee was as follows; pattern II (punctate pattern) in 16 patients, pattern I (thin hyper-echoic bands) in 6 patients and pattern III (homogeneous hyper echoic nodular or oval deposits) alone in 2 patients.

Therefore, pattern II was the most common pattern of calcification found among our patients. In agreement with our results, **Ellabban *et al.*** [14] revealed that the pattern II was the most common pattern of calcification found in the study.

In the current study, in 12 patients, US-identified calcifications defined as deposits of another nature than CPPD deposits were found; "Double contour sign", which is characteristic of MSU crystals.

An obvious discrepancy between US and conventional radiography has been reported, which might be attributed to many factors; 1) The bi-dimensional nature of the images taken from conventional radiography together with the overlap of bones limits the whole cartilage assessment. 2) Any pathologic concomitant conditions, in this case knee OA, may impair the correct detection of the cartilage because of the relevant narrowing of joint space [15]. In agreement with our results, **Mohammed *et al.*** [9], found a similar difference between Plain radiology and US.

Addressing secondary outcomes, the study found insignificant differences between OA patients as regards the mean pain score (13.9 ± 1.9 without crystals, 14.1 ± 2.3 with crystals) and mean disability score (46.2 ± 8.5 without crystals, 48.1 ± 13.2 with crystals), with p value > 0.05, in respect of the sonographic diagnosis of crystal deposits.

However, the study found the mean stiffness score was significantly higher in the knee OA patients with crystal deposits (4.2±1.1 without crystals, 5.9±1.8 with crystals), with $p < 0.05$, suggesting inflammation with crystal deposits. From these findings, we could understand that subclinical crystal deposits in knees with OA might be associated with a significantly higher inflammatory component.

In the current study, we used the presence of crystals on SF analysis as a reference method to determine the diagnostic test properties of CR and US in the detection of pathological findings indicative of crystals in patients.

US showed a high specificity with acceptable sensitivity to detect crystals in patients 93.8% and 83.3%, respectively. Our results are in agreement with a recent meta-analysis by **Gamon *et al.*** [16] and previous studies by **Lamers-Karnebeek *et al.*** [17].

To date, specificity and sensitivity of chondrocalcinosis in CR for the diagnosis of CPP crystals is not well established. Our study showed a good specificity 90.2% but lower sensitivity 22.2%.

Furthermore, despite the fact that US is considered to be an operator-dependent technology with poor repeatability, it is reassuring to see that previous studies have established moderate to good inter-observer reliability [18].

CONCLUSION

From ongoing results of our study, it could be concluded that musculoskeletal US was able to diagnose more patients with crystal deposits with high specificity and acceptable sensitivity compared to plain radiography in the studied group with knee OA.

Sonographic diagnosis of crystal deposition significantly correlated to stiffness scores in the study group. The presence of crystal deposits has contributed to a higher level of inflammation in patients with knee OA.

There was a significant relation between crystals identified by US and the presence of inflammatory components such as bursitis and effusion.

Although synovial fluid analysis by polarizing microscopy for identification of crystals is the most accurate, reliable, and direct method for diagnosis of crystals deposition, US is a useful noninvasive diagnostic tool with good sensitivity and specificity as shown in our study.

We believe that this study is a practical model for the potential benefit of routine use of diagnostic musculoskeletal ultrasound in patients with knee joint pain that might serve to screen for crystal deposits within the knee joints aiming to guide therapeutic regimens and response to different therapies.

RECOMMENDATION

We recommend doing US examination for any patient of OA presented with joint effusion in cases suspected to have crystals induced pathology prior to proceeding to needle aspiration for synovial fluid analysis and identification of crystals by polarizing microscopy.

It is better to keep needle aspiration for cases with no characteristic findings of calcification that found in US examination or in patients in need for therapeutic injection. Furthermore, US is recommended to guide difficult joint aspirations.

Review of these data potentially supports the use of ultrasonography as a better alternative to screen for crystal deposits aiming to properly address the magnitude of the problem in daily practice using a non-invasive, easy-to perform radio-diagnostic technique.

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