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# Articular and periarticular spinal calcifications in relation to synovial fluid findings in patients with calcium pyrophosphate dihydrate deposition disease (CPPD)

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## Abstract

**Background:** Calcium pyrophosphate dihydrate deposition disease (CPPD) is the second most common form of the crystal-associated arthritis. Diagnosis is achieved by detection of crystals by polarized light microscopy and/or detection of hyaline cartilage or fibrocartilage calcifications characteristic of CPPD deposition by musculoskeletal ultrasound (MSUS). Axial involvement with intervertebral disc calcification, sacroiliac erosions, and sub-chondral cysts of the facet joints occurs with CPPD deposition.

**Aim:** To assess the presence and relation between calcification of intervertebral discs, other articular and periarticular spinal structures, and synovial fluid analysis (SFA) and MSUS calcifications in patients with CPPD deposition disease.

**Methods:** One hundred patients with CPPD disease diagnosed according to the modified proposed diagnostic criteria by McCarty 1994 were included. Plain radiography on the spines, pelvis, and affected joints, MSUS on affected joints, and synovial fluid analysis (SFA) were done.

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**Results:** Spinal calcification was present in 55% of patients. The commonest site was anterior longitudinal ligament (43%). Characteristic CPPD calcifications by plain radiography on the knee and wrist joints were present in 38% and 16% respectively. Characteristic CPPD calcifications by MSUS on the knee and wrist joints presented in 93% and 27% respectively. CPPD crystal detection by SFA was 97%. The accuracy of MSUS to diagnose CPPD deposition disease is more than double that of plain radiography, and it is comparable to that of synovial fluid analysis. The result of intra-rater analysis between SFA by polarized light microscopy and MSUS was kappa 0.767 ( $p < 0.001$ ); this indicates substantial level of agreement between SFA and MSUS; between plain radiography and MSUS, it was kappa 0.188 ( $p = 0.32$ ) which indicates slight agreement, and between plain radiography and SFA, it was kappa 0.037 ( $p = 0.1$ ) which fails to reach a significant level of agreement. There was a significant positive relation between spinal calcification and wrist joint calcification by plain radiography.

**Conclusion:** Considerable spinal affection by CPPD deposition disease can be detected. Although the most definitive, reliable direct approach for CPPD deposition disease diagnosis is SFA using polarized light microscopy, MSUS is considered a useful non-invasive diagnostic tool in this situation. In CPPD deposition disease, MSUS has proven to be an excellent technique for detecting calcification in the articular tissue disease compared to conventional radiography.

**Keywords:** Calcium pyrophosphate dihydrate deposition disease (CPPD), Musculoskeletal ultrasound, Spinal calcification, Synovial fluid analysis

## Background

Calcium pyrophosphate dihydrate deposition (CPPD) disease is common in which CPPD crystals deposit within the joint leading to calcification [1–3]. McCarty and co-workers first identified CPPD crystals [4]. The crystals were found in the synovial fluid of patients without sodium urate crystals who had gout-like symptoms. This phenomenon was later described as “pseudogout” and radiologically defined by prominent multifocal calcifications in the articular cartilages and intervertebral disc spaces [5].

The CPPD crystals are observed to have weaker birefringence using polarized light microscopy as opposed to the stronger birefringence of mono-sodium urate (MSU) crystals. Radiographical diffraction or electron probe analysis best determines the exact nature of these crystals [6]. The gold standard for diagnosis of CPPD deposition disease is the identification of CPPD crystals using the compensated polarized light microscopic examination of the synovial fluid in the absence of joint infection or other cause of arthritis, particularly for acute conditions [7, 8].

High-frequency musculoskeletal ultrasound (MSUS) has been shown to be an outstanding tool for the accurate assessment of articular and juxta-articular changes and calcific deposits in crystal-induced diseases. MSUS is a sensitive and specific method in the evaluation of patients with chondrocalcinosis [3, 9].

Axial involvement with intervertebral disc calcification, sacroiliac erosions, and sub-chondral cysts of the facet joints occurs with CPPD deposition disease [10]. CPPD deposits within the ligamentum flavum or the transverse ligament of the atlas can be sizable and can progress,

causing cervical canal stenosis, cervical myelopathy, and foramen magnum syndrome. Odontoid fracture due to the calcification of the atlantoaxial joint may occur in CPPD deposition disease [11].

The aim of this study was to assess the presence and relation between calcification of intervertebral discs, other articular and periarticular spinal structures, and synovial fluid analysis findings and musculoskeletal ultrasound calcifications in patient with CPPD.

## Methods

### Study design: cross-sectional observational study

One hundred patients diagnosed as CPD crystal deposition disease according to the modified proposed diagnostic criteria by McCarty 1994 [12, 13] from outpatient clinics of rheumatology, with knee effusion candidate for aspiration, were included. The exclusion criteria are as follows: autoimmune disease, diabetic patients, renal osteodystrophy, hypothyroidism, hyperparathyroidism, hypervitaminosis D, idiopathic hypercalcemia, hemochromatosis, and diffuse idiopathic skeletal hyperostosis. All patients had, through clinical examination, plain radiography for the spines (antero-posterior and lateral views), wrist joints (antero-posterior view), and knee joints (antero-posterior view), searching for punctate and linear radiodensities in intervertebral discs, fibrocartilage, and hyaline or articular cartilage and calcification of spinal ligaments.

Conventional gray-scale ultrasound was performed using a 10–18-MHz linear scanner and middle-class to high-end machine ultrasound device (ACUSON X700 Ultrasound System - Siemens, America). Examination was carried out for the knee and wrist joints bilaterally

both longitudinal and transverse scans on cartilage (hyaline cartilage of the femoral condyles) and fibrocartilage (triangular fibrocartilage of the wrist and meniscus) searching for CPPD deposits ultrasonographically. CPPD deposits are hyperechoic that present in various patterns: pattern I, thin hyperechoic bands parallel to the surface of the hyaline cartilage; pattern II “punctate pattern,” consisting of multiple thin hyperechoic spots; and pattern III, homogeneous nodular or oval hyperechoic deposits, mostly mobile, found in bursae and articular recesses [14]. Synovial fluid analysis was done for all patients using polarized light microscopy for detection of CPPD crystals by an expert. The same operator performed the MSUS and SF analysis.

### Statistical analysis

The data was analyzed using the statistical package for the social sciences program (SPSS Inc., Chicago, IL, USA) version 16.0. Categorical and quantitative variables were respectively defined as numbers/percentage (%) and mean  $\pm$  SD. The Mann-Whitney or chi-square ( $\chi^2$ ) tests compared variables. The intra-rater reliability

(single rater and two replications) was assessed using the kappa coefficient of Cohen. A kappa value 0.01–0.20 was considered slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, and 0.81–0.99 almost perfect agreement. The statistical significance level was set at a  $p$  level lower than 0.05. Sensitivity and specificity of plain radiography and musculoskeletal ultrasonography for the detection of calcification were calculated using the formula:

$$\text{Sensitivity} = \frac{\text{Diseased persons with positive test}}{\text{All diseased persons}} \times 100$$

$$\text{Specificity} = \frac{\text{Non diseased persons with negative test}}{\text{All non - diseased persons}} \times 100$$

### Results

Out of the 100 patients with CPPD deposition disease included in the study, 42 were males (42%) and 58 were females (58%); their age ranged from 43 to 80 years with a mean of  $62.2 \pm 4.5$  years; and disease duration ranged from 0.1 to 12 years with a mean of  $14.5 \pm 3.1$  years.

**Table 1** Characters of CPPD deposition disease patients, plain radiography, and MSUS detection of calcifications and synovial fluid finding of CPPD crystals in studied group

Parameter mean $\pm$ SD and/or n (%)	CPPD patients n = 100
Age (years)	62.2 $\pm$ 4.5
Gender F to M	58:42
Disease duration (years)	14.5 $\pm$ 3.1
Plain radiography	
	<b>Spinal calcification</b>
	Intervertebral disc calcification
	16 (16)
	Anterior longitudinal ligament
	43 (43)
	Posterior longitudinal ligament
	20 (20) 3 (3)
	Ligamentum flavum
	38 (38)
	<b>Knee calcification</b>
	16 (16)
	<b>Wrist calcification</b>
Musculoskeletal ultrasound	
	<b>Knee calcification</b>
	93 (93)
	Pattern of calcification
	Pattern I
	55 (55)
	Pattern II
	67 (67)
	Pattern III
	10 (10)
	<b>Wrist calcification</b>
	27 (27)
	Pattern of calcification
	Pattern I
	3 (3)
	Pattern II
	26 (26)
	Pattern III
	0
Synovial fluid finding of CPPD crystals	(97)

On conventional radiography, spinal calcification was found in 55 patients (55%); the commonest site was anterior longitudinal ligament (43%), posterior longitudinal ligament (20%), intervertebral disc (16%), and ligamentum flavum (3%). Meniscal calcification was found in 38 patients (38%); triangular fibrocartilage calcifications of the wrist were found in 16 patients (16%)

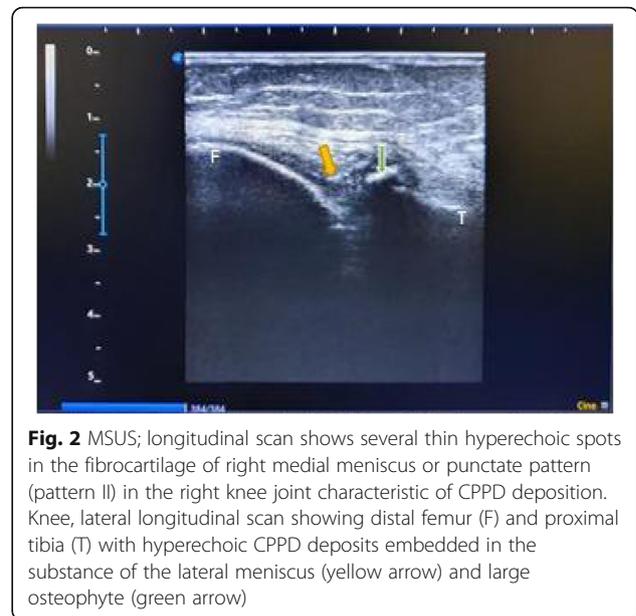
MSUS showed CPPD calcifications in the menisci, femoral hyaline cartilage, and bursae and articular recesses in the knee joint in 93 patients (93%) and in the triangular fibrocartilage of the wrist in 27 patients (27%)

Three patients out of 100 patients (3%); CPPD crystals could not be detected by synovial fluid analysis by polarized light microscopy, but could be shown by MSUS

Characteristic features of CPPD crystal deposition disease patients are presented in Table 1. On conventional radiography, spinal calcification was found in 55 patients (55%) (Fig. 1a); the commonest site of spinal calcification in studied CPPD deposition disease patients were anterior longitudinal ligament (43%) followed by posterior longitudinal ligament (20%), intervertebral disc (16%), and lastly ligamentum flavum (3%); and it was noticed that more than one site of calcification was found in some patients. Meniscal calcification was found in 38 patients (38%) (Fig. 1b), and triangular fibrocartilage calcifications of the wrist were found in 16 patients (16%) (Table 1). MSUS examination showed that CPPD calcifications characteristic of CPPD deposition was found in the menisci, femoral hyaline cartilage, and bursae and articular recesses in the knee joint in 93 patients (93%) and in the triangular fibrocartilage of the wrist in 27 patients (27%). The commonest pattern of knee joint calcification in the studied CPPD deposition disease patients was pattern II in 62 patients (67%) (Fig. 2) followed by pattern I in 51 patients (55%) (Fig. 3) and lastly pattern III in 9 patients (10%). More than one site of calcification was found in some patients. In the wrist joint, the commonest type was pattern II in 26 patients (26%) then pattern I in 3 patients (3%) (Fig. 3) (Table 1).

It was found that in three patients out of 100 patients (3%), CPPD crystals could not be detected by synovial fluid analysis by polarized light microscopy, but could be shown by MSUS. CPPD crystals by polarized microscopy are shown in Fig. 4.

Figure 5 presents the percent of the diagnosis of CPPD deposition disease by synovial fluid analysis, MSUS, and conventional plain radiography. The accuracy of MSUS to diagnose CPPD deposition disease is more than



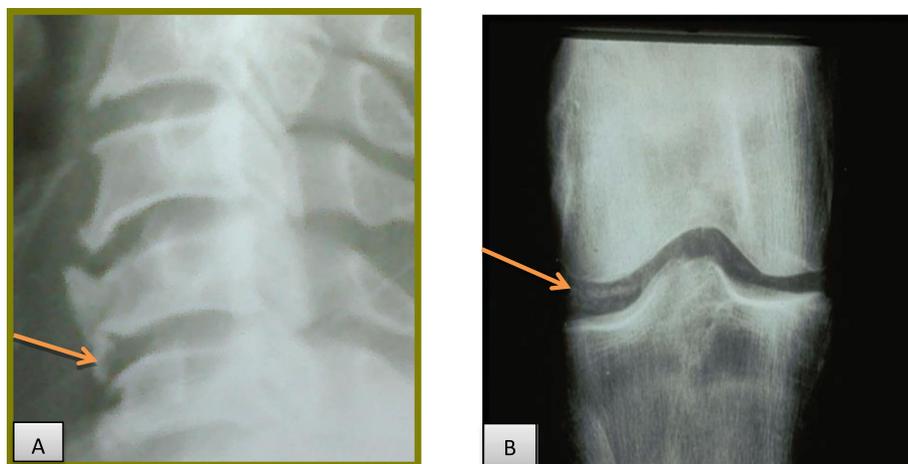
**Fig. 2** MSUS; longitudinal scan shows several thin hyperechoic spots in the fibrocartilage of right medial meniscus or punctate pattern (pattern II) in the right knee joint characteristic of CPPD deposition. Knee, lateral longitudinal scan showing distal femur (F) and proximal tibia (T) with hyperechoic CPPD deposits embedded in the substance of the lateral meniscus (yellow arrow) and large osteophyte (green arrow)

double that of conventional radiography, and it is comparable to that of synovial fluid analysis.

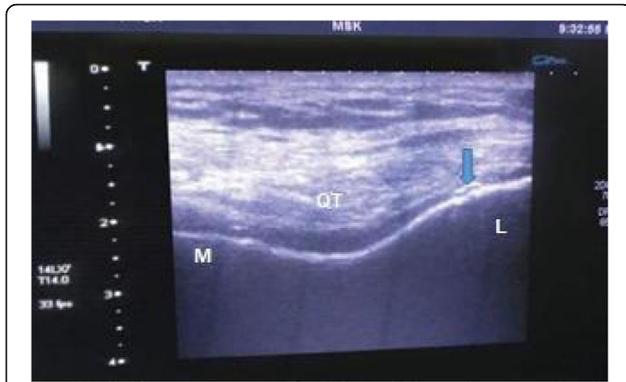
In patients with CPPD crystals, the sensitivity of MSUS for calcification detection was 95.8% while that of conventional radiography was 39.2%, while the specificity was 100% for both MSUS and conventional radiography for calcification detection.

In three of the cases, CPPD crystals could not be detected by synovial fluid analysis by polarized light microscopy, but MSUS showed characteristic features of CPPD crystal deposition disease.

The result of intra-rater analysis between SFA by polarized light microscopy and MSUS for detection of CPPD calcification was kappa 0.767 ( $p < 0.001$ ); this



**Fig. 1** a Plain X-ray, lateral view of on cervical spine shows anterior longitudinal ligament calcification (arrow). b Plain radiography of the knee joint showing chondrocalcinosis (arrow)



**Fig. 3** MSUS; transverse scan shows thin hyperechoic band parallel to the surface of the hyaline cartilage (pattern I) in the femoral condyle characteristic of CPPD deposition. Knee, suprapatellar transverse scan in full flexion. Convex bony contour of femoral condyle is the deepest structure. A bright, hyperechoic band of CPPD deposition (arrow) is seen embedded in the dark, anechoic to hypoechoic hyaline cartilage that covers the femoral condyle. L, lateral; M, medial; TQ, quadriceps tendon

indicates substantial level of agreement between SFA and MSUS; however, between conventional radiography and MSUS, it was kappa 0.188 ( $p = 0.32$ ) which indicates slight agreement, and between conventional radiography and SFA, it was kappa 0.037 ( $p = 0.1$ ) which fails to reach a significant level of agreement.

Table 2 presents the relation between the presence of spinal calcification in patients with CPPD deposition disease and the presence of calcifications characteristic of CPPD deposition in the knee and wrist joints detected by conventional plain radiography and MSUS. There was a significant positive association between spinal calcification and wrist joint calcifications by conventional radiography.

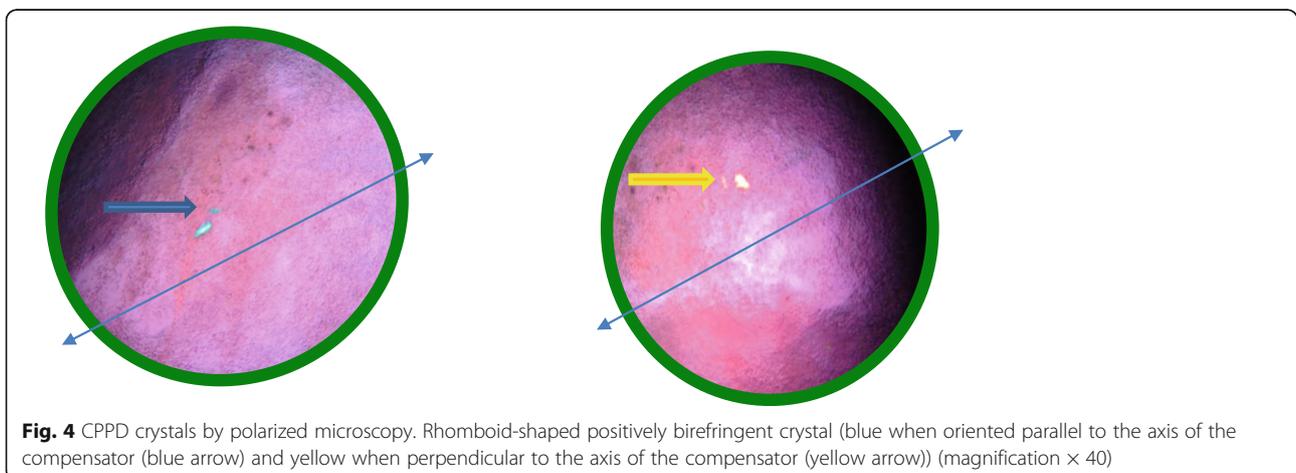
## Discussion

The second most common type of the crystal-induced arthritis is detected as calcium pyrophosphate dihydrate

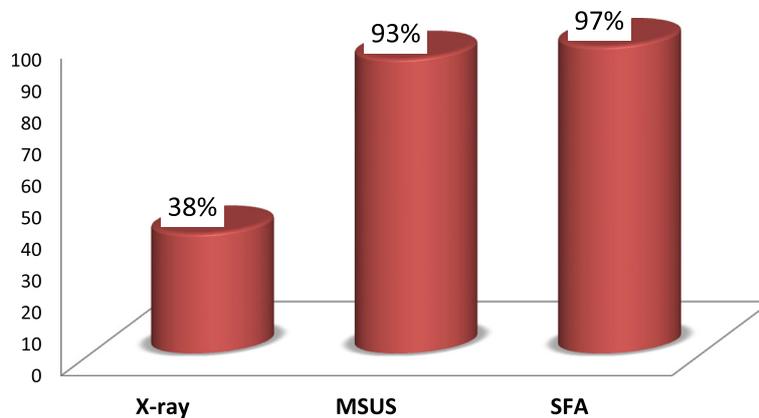
deposition disease [10]. The clinical presentation of CPPD can vary from asymptomatic to acute or chronic inflammatory arthritis, with a variety of symptoms and signs similar to those seen in cases of gout or other forms of inflammatory arthritis or septic arthritis making it difficult to distinguish clinically between CPPD disease and other joint-affecting conditions. About 25% of patients presented with acute pseudogout, rheumatoid-like appearance accounts for less than 5% of patients with CPPD disease, and more than 50% of patients with CPPD disease have symptoms like osteoarthritis [15–18]. In those who develop arthritis symptoms, physical examination has little value in the diagnosis and its consequences [8, 19].

Diagnosis is confirmed by using polarized microscopy and the identification of crystals in the synovial fluid [7] or the detection of the characteristic calcification of CPPD crystal deposition (chondrocalcinosis) in the conventional plain radiography and/or high-resolution MSUS to detect hyaline articular cartilage or fibrocartilage calcifications [8]. Axial involvement with intervertebral disc calcification, sacroiliac erosions, and subchondral cysts of the facet joints occurs with CPPD deposition disease [10].

In our study, we found that incomplete spinal calcification was present in 55 patients (55%) of all patients. It was higher than that noticed by Salaffi and co-workers [20] where conventional radiographs showed spinal calcifications in 17 patients (34.7%), but their study was done on the cervical spine only (conventional radiographs of the upper cervical spine only were performed), other spine regions were not examined, patients had a higher age (range 66–88, mean age  $70.4 \pm 6.8$  years) in comparison to our study. On the contrary, the study of Sekijima and co-workers [21] showed that 100% of fourteen patients had cervical spine calcifications; this difference may be related to the older age of patients included in their study (range 54 to 92 with mean  $\pm$  SD,  $77.5 \pm$



**Fig. 4** CPPD crystals by polarized microscopy. Rhomboid-shaped positively birefringent crystal (blue when oriented parallel to the axis of the compensator (blue arrow) and yellow when perpendicular to the axis of the compensator (yellow arrow)) (magnification  $\times 40$ )



**Fig. 5** Percent of the diagnosis of CPPD deposition by conventional plain radiography, MSUS and synovial fluid analysis. The accuracy of MSUS to diagnose CPPD calcification is more than double that of X-ray, and it is comparable to that of synovial fluid analysis

8.5). Moreover, computed tomography was used, not conventional radiography as in our study, and their study was done on the cervical spines only. Our values are also lower than the research done by Finckh and co-workers [22] where cervical calcifications were found in 24 out of 35 patients (69%) in the CPPD based on computed tomography beside conventional radiography.

Chondrocalcinosis (intervertebral disc calcification) was noted in 16 patients (16 %) in our study, in agreement with results of the study done by Gruber and co-workers [23], which was based on histologic features with special attention to crystal deposition of intervertebral disc (cervical, lumbar, and lumbosacral); they showed that 14.69% (31 out of 211 patients) of the specimens were positive for the presence of crystals, although this is histological study, but the mean age was lower than that of our study, which was 35 ± 11.8 years. Also, in the study population of Berlemann co-workers [24], the histopathological study of postoperative degenerated lumbar discs showed that CPPD crystal deposition was

found in 15.7% of the investigated patients (12.6% of discs).

In our study, comparison between MSUS and SFA to diagnose CPPD deposition disease showed that MSUS diagnoses CPPD deposition disease in the joint in 93 patients (93%) which was higher than that noticed by Foldes [25], which was 89%, but the studied patients in this research was small in number (21 patients against 100 in our study); also, the transducer frequency used was 5–10 MHz, whereas in our study, it was 10–18 MHz.

In the current study, the sensitivity of ultrasonography for detection of calcification in patients with CPPD crystals was 95.8% while that of plain radiography was 39.2%. In the study done by Filippou and co-workers [26], the sensitivity of MSUS to diagnose CPPD deposition disease was 96.4%. In the study by Ellabban et al. [18], they found that the MSUS sensitivity was 84.2% for the detection of CPPD calcification, while it was 13% for conventional radiography. In their study, sixty patients

**Table 2** Relation between the presence of spinal calcification and the presence of calcifications characteristic of CPPD deposition in the knee and wrist joints detected by conventional radiography and MSUS in the studied patients

Calcification	Spinal calcification		Spinal calcification		$\chi^2$	p
			Present n (%)	Absent n (%)		
Plain X-ray	Knee	Present	20 (37)	18 (40)	0.091	0.763
		Absent	35 (63)	27 (60)		
	Wrist	Present	13 (24.1)	3 (6.7)	5.489	<b>0.019</b>
		Absent	42 (75.9)	42 (93.3)		
MSUS	Knee	Present	51 (92.6)	42 (93.3)	0.002	0.866
		Absent	4 (7.4)	3 (6.7)		
	Wrist	Present	18 (31.5)	9 (20)	1.671	0.196
		Absent	37 (68.5)	36 (80)		

There was significant positive association between spinal calcification and wrist joint calcifications detected by conventional radiography

with knee effusion were included; their age ranged from 25 to 70 years with a mean of  $49 \pm 9.3$  years; searching for the presence of CPPD crystals, they found CPPD crystals in synovial fluid in 32/60 patients (53.3%), and they had also calcification characteristic of CPPD in MSUS evaluation; however, plain radiographic calcification characteristic of CPPD was found only in 5 patients with ultrasonically defined CPPD calcifications knee joint. The difference from the current study may be due to the small number of CPPD patients included in their study (32 patients versus 100); also, the transducer frequency used was 7.5–12 MHz, whereas we used a higher transducer frequency (10–18 MHz).

The presence of CPPD crystals in synovial fluid certainly confirm the diagnosis, based on standard diagnostic criteria for CPPD crystal deposition disease, but a negative microscopic test does not preclude it [12, 13].

## Conclusions

Considerable spinal affection by CPPD deposition disease can be detected. Although the most definitive, reliable direct approach for CPPD deposition disease diagnosis is SFA using polarized light microscopy, MSUS is considered a useful non-invasive diagnostic tool in this situation. In CPPD deposition disease, MSUS has proven to be an excellent technique for detecting calcification in the articular tissue disease compared to conventional radiography.

## Strength of the study

The strength of the study is as follows: three cases, in which CPPD crystals could not be detected in synovial fluid by polarized light microscopy, but MSUS showed characteristic features of CPPD crystal deposition disease (probable diagnosis) which raises the diagnostic value of MSUS and so reflects the importance of use of MSUS in diagnosing CPPD deposition disease.

## Limitations of the study

The limitations of the study are as follows: the small number of the studied population, not considering other causes of calcification other than CPPD deposition disease, and not considering the presence of other types of crystals. The MSUS is time consuming when searching for every site for calcification.

## Abbreviations

CPPD deposition disease: Calcium pyrophosphate dihydrate deposition disease; MSUS: Musculoskeletal ultrasound; SFA: Synovial fluid analysis

## Acknowledgements

Not applicable.

## Authors' contributions

MIA, ASE, AHI, MMR, and RAA prepared the study design. RAA and AHI contributed to the data acquisition and analyzed and interpreted the patient data. RAA performed the synovial fluid analysis and musculoskeletal

ultrasound and was a major contributor in writing the manuscript. All authors have read and approved the manuscript.

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics approval and consent to participate

This study is a thesis and is an extension of my previous published study in *Rheumatology International*.

## Consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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