Formosan Journal of Rheumatology 2009;23:25-32

Original Article

Evaluation of calcium pyrophosphate dihydrate deposition disease by ultrasound

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Objective: Our aim was to characterize the ultrasonographic features of patients with calcium pyrophosphate dihydrate (CPPD) deposition disease, and compare X-ray and ultrasound in evaluating CPPD deposition disease.

Methods: In this retrospective study, all 71 patients between 2004 and 2007 with CPPD deposition disease proved by microscopic synovial fluid analysis were enrolled. We collected and analyzed 38 patients of those, on whom both conventional X-ray and high-resolution ultrasound had been carried out.

Results: All patients were elderly (i.e. >65 y/o) and mostly coexisted with osteoarthritis. The involvement of knee joint was the most common site. Popliteal cyst was detected in 9 of 71 patients. Synovial fluid analysis of 38 patients with CPPD deposition disease revealed that the average total white cell count was 25592.1 ± 16697.8 /mm^3, with significant neutrophil predominance. There was significant evidence that ultrasound was more reliable than X-ray in the diagnosis of CPPD deposition disease (p=0.002). Besides, there were no patients with CPPD deposition disease in whom X-rays suggested CPPD deposition disease, but for whom ultrasound results were negative.

Conclusion: We found that bright stippled foci in the synovial fluid or around the articular region, the thin hyperechoic band parallel to the surface of the hyaline cartilage, and the calcification of fibrocartilage seen on ultrasound could represent CPPD deposits. Our data showed that ultrasound is a useful and important tool in the diagnostic investigation of patients with CPPD deposition disease.

Key words: Ultrasound, calcium pyrophosphate dihydrate, pseudogout, chondrocalcinosis, synovial fluid analysis

Introduction

Calcium pyrophosphate dihydrate (CPPD) deposition disease is a type of inflammation of the joints that is caused by deposits of CPPD crystals in and around the joints. It usually affects one joint at a time, but sometimes affects several joints at once [1]. CPPD deposition disease has distinct appearances when the synovial fluid is viewed under a polarized-light microscope; this makes it possible to precisely identify the cause of the joint inflammation when synovial fluid is available [2]. In other words, the most reliable diagnosis of CPPD deposition disease is synovial fluid analysis.

Imaging modalities–plain X-ray–can provide helpful

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Received: August 5, 2008
Revised: September 29, 2008
Accepted: October 9, 2008

clues in the diagnosis of CPPD deposition disease, if there is no synovial fluid available [3]. However, it cannot assess early soft tissue changes such as minimal effusion, synovial proliferation, local hypervascularization, early erosions, and the development of popliteal cyst (i.e. Baker's cyst). Ultrasound is rapidly becoming popular among rheumatologists for the differential diagnosis of rheumatic disease, particularly in crystal-induced arthritis [4].

To our knowledge, no ultrasonographic evaluation of CPPD deposition disease has been conducted in Taiwan. The aim of our study is to investigate diagnostic imaging that could help provide an in-depth understanding of CPPD disease.

Materials and Methods

Patients and subjects

In this retrospective study, we reviewed all patients with a definitive diagnosis of CPPD deposition disease at the Tri-Service General Hospital between January 2004 and December 2007. The database recorded the diagnoses of all patients with CPPD deposition disease based on the typical intracellular and extracellular birefringent rod-shaped crystals in the synovial fluid [1]. The ultrasound examinations and arthrocenteses of all patients were carried out by rheumatologic specialists.

Diagnostic imaging

X-ray examinations of clinically involved sites were performed in conventional non-weight-bearing radiographs with antero-posterior and lateral projections, using modern systems (digital luminescence radiography, Agfa). Ultrasound examinations were performed using high-quality broadband linear transducers with a frequency range of 8–14MHz (Philips EnVisor series ultrasound system). Cartilage was examined in longitudinal and transverse scanning. The whole popliteal area was also scanned during the evaluation of the posterior hyaline cartilage of the knee.

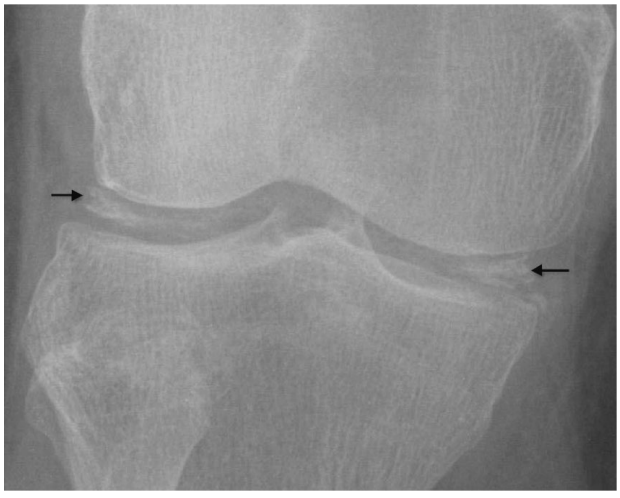

Figure 1. Knee radiograph showing meniscal calcification (arrow).

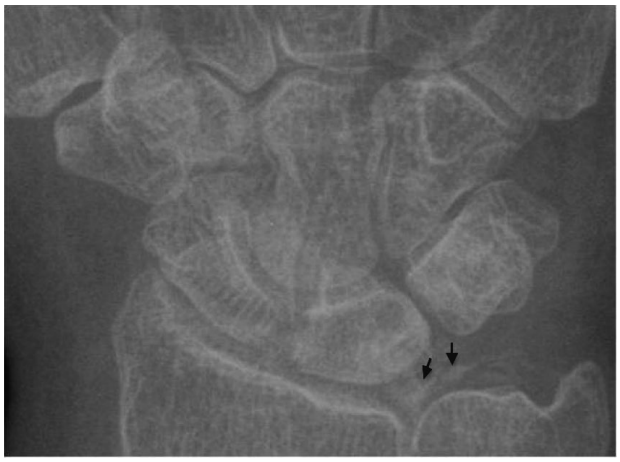

Figure 2. Wrist radiograph showing calcification in the triangular fibrocartilage complex (arrow).

X-ray findings highly suggestive of CPPD deposition disease–which we have taken into consideration in this study–included punctate and linear radiodensities in fibrocartilage and hyaline or articular cartilage (chondrocalcinosis) [3] (Fig. 1 and 2).

The ultrasound findings suggestive of CPPD deposition disease analyzed in this study included bright stippled foci [8,9] (Fig. 3A, 3B, 3C, and 3D), the thin hyperechoic band parallel to the surface of the hyaline cartilage [4,6-11] (Fig. 4 and 5), and the calcification of fibrocartilage [4,6-11] (Fig. 6A and 6B).

All images from each method applied were independently reviewed by one experienced radiologist; thereafter, the same opinion on each imaging sign was obtained.

Synovial fluid analysis

All synovial fluid analyses were performed by one experienced medical technologist; calcium pyrophosphate dihydrate crystal was identified using the polarized-light microscope (Carl Zeiss, Axioskop, EL-Einsatz).

Statistical Analysis

A McNemar test was used to test the significance of differences between ultrasound and X-ray as imaging methods vis-a-vis CPPD deposition disease. P values

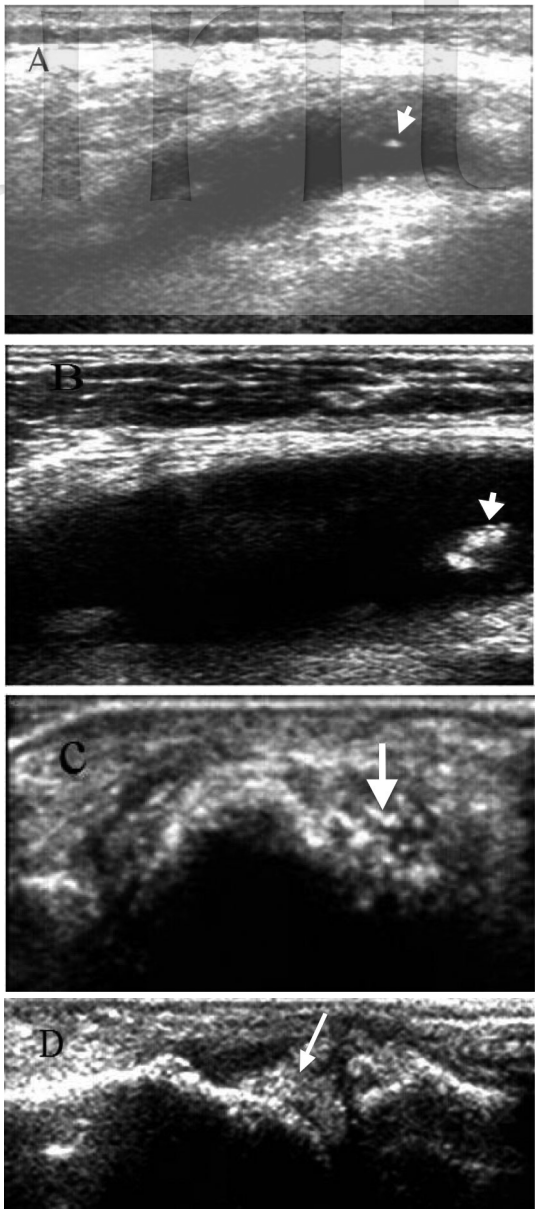

Figure 3. Bright stippled foci. (A) Hypoechoic fluid with a hyperechoic and floating spot (arrow) in the longitudinal ultrasound of the knee joint. (B) Hypoechoic fluid with some large floating spots (arrow) in the longitudinal ultrasound of the knee joint. (C) Hyperechoic spots deposition (arrow) in the longitudinal ultrasound of the first metatarsophalangeal joint. (D) Hyperechoic spots deposition (arrow) in the longitudinal ultrasound of the second metacarpophalangeal joint.

less than 0.05 were considered significant.

Statistical analysis was performed by using the Statistics Package for Social Science (SPSS) software, version 12 for Microsoft Windows.

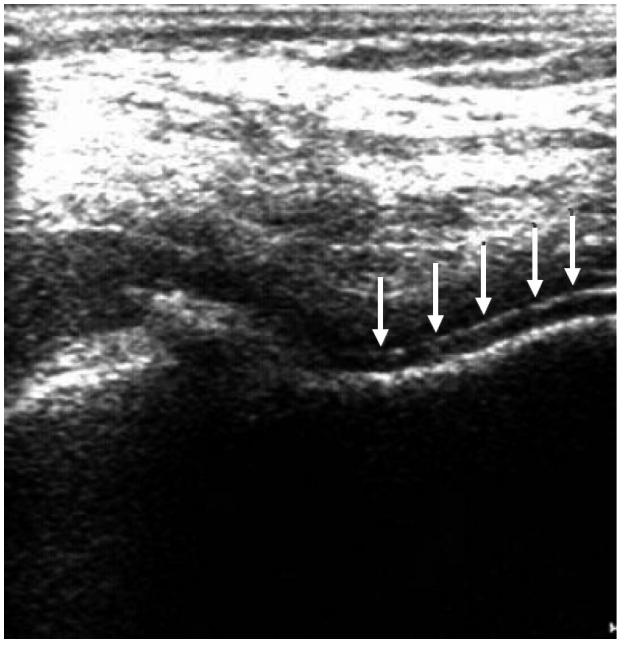

Figure 4. The thin hyperechoic band (arrow) parallel to the surface of the hyaline cartilage in the transverse ultrasound of the femoral condyle.

Results

Seventy-one patients, each with a definitive diagnosis of CPPD deposition disease, were enrolled in this study. Forty-three of the patients were female (60.6%). We found a total of 82 involved sites; the involvement of knee joint was the most common (61/82, 74.4%). Popliteal cysts were detected in nine patients (9/71, 12.7%); typical CPPD crystals were demonstrated in six of those (Fig. 7). The distribution of clinically involved sites in patients with CPPD deposition disease is summarized in Table 1.

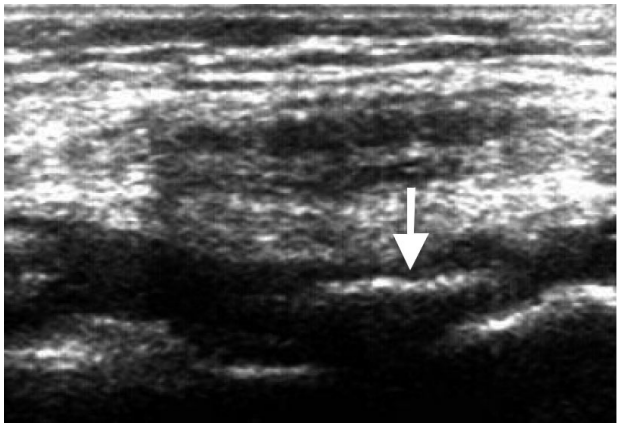

Figure 5. The fragmented hyperechoic band (arrow) with acoustic shadow parallel to the surface of the hyaline cartilage in the transverse US of the femoral condyle.

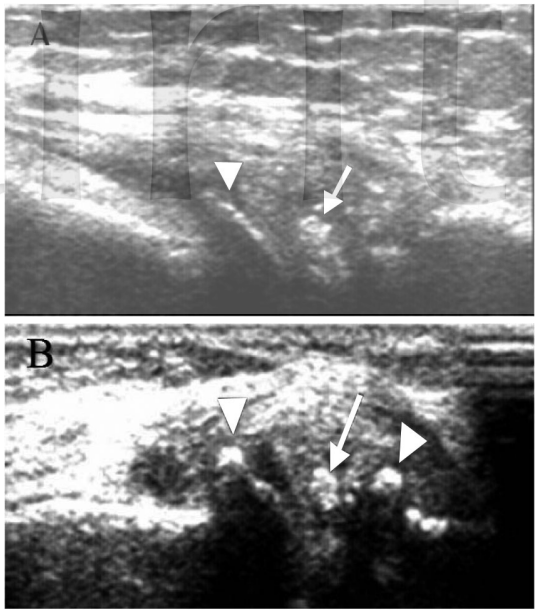

Figure 6. Calcification of fibrocartilage. (A and B) Meniscal calcification of the knee (arrow) and osteophyte formation (arrowheads) in the longitudinal ultrasound.

Among the 71 patients with CPPD deposition disease, 38 patients underwent both X-ray and ultrasound examinations; females were predominant within this subgroup (27/38, 71.1%). All patients were elderly (>65 y/o) and coexisted with osteoarthritis, up to 94.7%. There also appeared to be a characteristic distribution of involved sites in the knee joint. The average of symptom duration of arthritis through to arthrocentesis was 2.8 ± 2.3 days. Synovial fluid analyses of 38 patients with CPPD deposition disease revealed that the average total white cell count was 25592.1 ± 16697.8 /mm^3 with significant neutrophil predominance. Gram stains and cultures of the fluids obtained by arthrocentesis were negative for infectious organisms. The demographic and clinical characteristics of those patients are listed in Table 2.

Table 1. Distribution of all 82 clinically involved sites in 71 patients with CPPD deposition disease

Involved sites	No. of sites
Lower extremities (n=75)	
MTP-I joint	1
Ankle	4
Knee	61
Popliteal cyst	9
Upper extremities (n=6)	
MCP-II joint	1
Wrist	3
Elbow	3

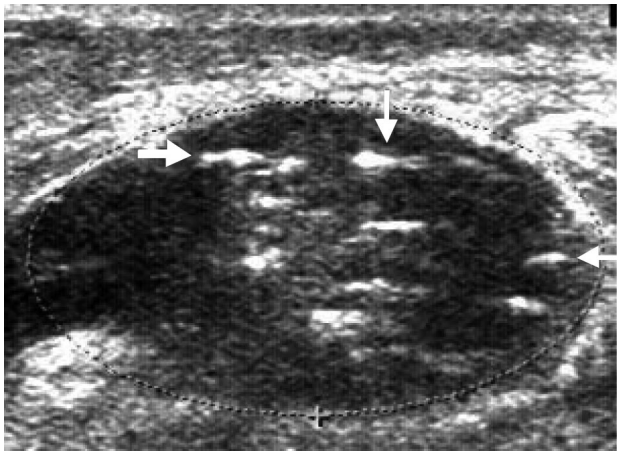

Figure 7. Small hyperechoic foci (arrows) in the Baker's cyst proved to be CPPD crystals, as verified by testing the aspirated fluid.

Ultrasound findings seen mainly in the joints included the following: bright stippled foci in the synovial fluid or around the articular region, the thin hyperechoic band parallel to the surface of the hyaline cartilage, and the calcification of fibrocartilage in nine, 14, and 22 of the 38 patients with CPPD deposition disease, respectively. These signs were compared with the signs of X-ray, to determine comparative diagnostic accuracy; these results are shown in Table 3. Plain film radiography revealed chondrocalcinosis in 18 of 38 patients with CPPD deposition disease (47.4%), but at least one positive sign was found in the ultrasound findings of 30 of 38 patients with CPPD deposition disease (78.9%). Thus, we found that ultrasound was more reliable than X-ray examinations in the evaluation of CPPD deposition disease (p=0.002).

There were no patients with CPPD deposition disease in whom X-rays were suggestive of CPPD deposition disease but ultrasound was negative. In eight of 38 patients with CPPD deposition disease (21.1%), ultrasound failed to reveal specific signs. Nevertheless, ultrasound revealed increased echo-free fluid in the joint space, synovial proliferation, or hypervascularization by way of color Doppler examination. These sites of eight different patients included five knees, one elbow, one wrist, and one ankle.

Discussion

CPPD deposition disease is one of the most common crystal arthropathies, but the majority of patients are probably asymptomatic [5]. Even in those who develop arthritis symptoms, a physical examination has little

Table 2. Demographic and clinical characteristics of 38 CPPD deposition disease patients with both X-ray and ultrasound examinations.

No	Gender	Age	Location	Symptom Duration (D)	Coexist with OA	WBC in SF	PMN (%) in SF
1	F	84	Knee, R+L	2	Y	73,600	100
2	F	80	Wrist, L	3	Y	13,200	89
3	F	73	Knee, R+L	1	Y	26,400	99
4	F	69	Knee, R+L	10	Y	34,600	95
5	F	84	Knee, L	1	Y	27,200	99
6	M	86	Elbow, L	2	N	44,800	99
7	F	88	Elbow, L	2	Y	7,200	76
8	M	83	Knee, L	1	Y	27,800	95
9	F	77	Knee, R+L	1	Y	24,600	92
10	F	83	Knee, L	1	Y	27,200	90
11	F	79	Wrist, ankle & knee, R	3	Y	35,000	92
12	F	73	Knee, R+L	1	Y	13,400	86
13	F	78	Knee, R	7	Y	19,000	99
14	F	66	Knee, R	3	Y	6,400	91
15	M	75	Knee, R+L	2	Y	19,600	90
16	F	73	Ankle, R+L	4	Y	25,600	94
17	M	85	Knee, L	1	Y	5,000	90
18	F	88	Knee, L	4	Y	3,100	97
19	F	81	Knee, R	10	Y	45,200	100
20	F	78	Knee, R+L	6	Y	10,400	80
21	M	89	Wrist, L	1	Y	1,800	80
22	F	84	Knee, R	2	Y	30,800	97
23	M	83	Knee, L	2	Y	63,000	98
24	F	82	Knee, R+L	5	Y	2,300	92
25	F	94	Knee, L	4	Y	39,000	99
26	F	94	Knee, L	2	Y	38,600	93
27	M	83	Knee, L	1	Y	40,400	99
28	F	90	Knee, L	1	Y	42,400	94
29	F	74	Knee, L	1	N	27,200	87
30	F	85	Ankle, R+L	2	Y	28,300	91
31	F	84	Knee, R+L	3	Y	24,600	96
32	M	87	Knee, L	6	Y	14,000	97
33	M	80	Ankle, R	2	Y	1,200	78
34	M	86	Knee, L	3	Y	33,600	87
35	F	92	Knee, R	1	Y	12,200	95
36	M	78	Knee, R+L	2	Y	33,000	99
37	F	90	Knee, R+L	1	Y	11,200	97
38	F	82	Knee, R+L	1	Y	39,600	99
Mean	—	82.1 ± 6.7	—	2.8 ± 2.3	36/38 (94.7%)	25592.1 ± 16697.8	92.9 ± 6.4

Abbreviations: OA = osteoarthritis; SF = synovial fluid; WBC = white blood cell; PMN = polymorphonuclear cell

value in diagnosing CPPD deposition disease and its many consequences. X-ray is a quick, effective, and standard imaging method for the musculoskeletal system; therefore, it is usually the first imaging

Table 3. Comparison of diagnosis for CPPD deposition disease patients, between X-ray and ultrasound

Method	Sign	No. of patients	Percentage (%)	p (McNemar test)
Ultrasound	Bright stippled foci	9/38	23.7	—
	Hyperechoic band parallel to the surface of the hyaline cartilage	14/38	36.8	—
	Calcification of fibrocartilage	22/38	57.9	—
	At least one positive sign	30/38	78.9	0.002
X-ray	Chondrocalcinosis	18/38	47.4	

procedure in the investigation of disorders of this system, particularly in crystal-induced arthropathy [3]. X-ray can be the established imaging method in patients with CPPD deposition disease due to the characteristic sign, chondrocalcinosis. Typical calcifications in X-ray are punctate and linear radiodensities in fibrocartilage and hyaline or articular cartilage and, with lesser frequency, in bursae, ligaments, and tendons [3,12]. In any case, CPPD deposition disease is often associated with degenerative radiographic changes in joints, including subchondral cysts, osteophyte formation, joint-space narrowing, and bone and cartilage fragmentation [13], but these findings are by no means specific to CPPD deposition disease. Several authors have found X-rays in patients with CPPD deposition disease to be negative for a long time [12,14]. In a prospective study, Doherty et al. reported that initial X-rays did not show signs of CPPD deposition disease in 49% (51 of 104 patients) [14].

Over the past few years, there has been growing interest in ultrasound in European rheumatology [4,6-10]. There are some advantages to ultrasound, including its repeatability, high resolution, and dynamic assessment; as such, it is a method of guidance for invasive procedures. CPPD crystal material found in joints reflects ultrasound waves more strongly than surrounding tissues and thus can be easily distinguished [11]. There are several studies in the literature that described bright stippled foci in the synovial fluid or around the articular region, the thin hyperechoic band parallel to the surface of the hyaline cartilage, and the calcification of fibrocartilage as the important signs on ultrasound for CPPD deposition disease [4,6-11]. In one of these studies, Georgios et al. described that the sonography has demonstrated a high specificity (equal to 96.4%) and good sensitivity (equal to 86.7%) with a positive predictive value of 92% and a negative predictive value of 93% [6]. Based on the few existing publication [4,6-11], we considered as CPPD deposition disease that presented one of the above patterns on ultrasound. We also can observe the common findings of arthritis–including an increase in echo-free fluid in the joint space, synovial proliferation, or hypervascularization–via a color Doppler examination [15].

In addition to X-ray, we have undertaken high-resolution ultrasound investigations at our institution for over four years, for the purposes of diagnosing CPPD deposition disease patients and assisting in arthrocentesis procedures. Because ultrasound frequently shows distinctive signs of CPPD deposition disease–even among patients with negative X-ray findings–ultrasound has become a standard examination at our hospital. Nonetheless, making a diagnosis of CPPD deposition disease is still based upon a demonstration of the presence of CPPD crystals in aspirated joints or sites.

In the present study, our data were consistent with those of previous studies, in that the knee joint was the most common site of involvement and CPPD deposition disease occasionally coexisted with osteoarthritis in elderly patients [13,14,16]. We noticed that popliteal cysts developed in over 10% of patients with CPPD deposition disease; this finding is not uncommon, so the popliteal fossa should be examined thoroughly during a physical examination or detected definitively by ultrasound [17]. The average total cell counts in the synovial fluid samples in our study were 2,000-50,000 cells/mm^3; these cases were diagnosed as inflammatory arthritis, although cell counts over 50,000 cells/mm^3 in two patients and under 2,000 cells/mm^3 in two patients were noted. The finding was also consistent with the characteristic of CPPD deposition disease [5].

We evaluated high-resolution ultrasound and compared it to X-ray in terms of evaluating CPPD deposition disease. We found that in 12 of the 38 patients (31.6%) with CPPD deposition disease as identified by ultrasound, standard radiographs did not confirm the diagnosis. Furthermore, eight of 38 patients (21.1%) with CPPD deposition disease were proved by synovial fluid analysis, but ultrasound did not supply adequate information to diagnose CPPD deposition disease. There was still a significant difference between ultrasound and X-ray in evaluating CPPD deposition disease ($p=0.002$); however, the best diagnostic method of CPPD deposition disease should be synovial fluid analysis, as well as the viewing of typical intracellular and extracellular CPPD crystals under a polarized-light microscope. In our study, X-ray was used to diagnose CPPD deposition disease in less than 50% of cases. We thought that when only X-ray examinations had been used to evaluate CPPD deposition disease, osteoarthritis was easily the first consideration by clinicians if no chondrocalcinosis was found. Ultrasound investigations diagnosed 30% more cases, thus increasing the accuracy of ultrasound over X-ray examination in evaluating CPPD deposition disease. But we noticed that the percentage of the calcification of fibrocartilage was solely higher than the percentage of X-ray if "only, not at least" one positive sign on ultrasound compared with X-ray. So ultrasound examination should be performed in great detail during the procedure.

The utility of ultrasound in diagnosing knee chondrocalcinosis has been examined in only a few studies [4,6-11]. The important contribution of the

current study is that it used the presence of CPPD crystals in the synovial fluid as a "gold standard." The objective of this study was to evaluate the capacity of ultrasound to offer a diagnosis of CPPD deposition disease. Moreover, if CPPD deposition disease is still suspected and X-ray results do not confirm a diagnosis of CPPD, non-invasive ultrasound should be arranged for further study. Ultimately, the use of ultrasound as a primary tool for rheumatologists when there is suspected CPPD deposition disease makes the possibility of rapid diagnosis more likely.

In conclusion, we found bright stippled foci in the synovial fluid or around the articular region, the thin hyperechoic band parallel to the surface of the hyaline cartilage, and the calcification of fibrocartilage representing CPPD deposits, as seen on ultrasound, to be reliable features in the evaluation of CPPD deposition disease. Ultrasound is a useful and important tool for the diagnostic investigation of patients with CPPD deposition disease, even in the absence of joint effusion.

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藉由超音波評估雙氫氧化焦磷酸鈣沈積疾病

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目的：描繪在雙氫氧化焦磷酸鈣沈積疾病的病患裡所表現的超音波特徵，並且比較X光和超音波在評估雙氫氧化焦磷酸鈣沈積疾病上的區別。**方法：**在這回顧研究中，收集71位病患在2004年至2007年間經關節液證實罹患雙氫氧化焦磷酸鈣沈積疾病。分析其中38位皆接受X光和超音波檢查的病患。**結果：**全部病患皆為老年人(>65歲)並且大多數同時存在退化性關節炎。膝關節侵犯是最常見的位置。9位病患發現有腘窩囊腫。在38位雙氫氧化焦磷酸鈣沈積疾病的病患，關節液分析顯示總白血球細胞數的平均值是25592.1 ± 16697.8 /mm^{3}併嗜中性球占絕對多數。統計分析顯示超音波診斷雙氫氧化焦磷酸鈣沈積疾病比X光更具可信(p=0.002)。此外，我們並沒有病患的X光認為是雙氫氧化焦磷酸鈣沈積，但超音波是陰性的結果。**結論：**我們發現在超音波上看到明亮點刻狀的點在關節液裡或關節區周圍，薄的高回音條帶狀平行於透明軟骨表面，以及纖維軟骨鈣化可代表雙氫氧化焦磷酸鈣沈積。我們的數據顯示超音波是用於診斷性研究雙氫氧化焦磷酸鈣沈積疾病病患的一項有用且重要的工具。

關鍵詞：超音波、雙氫氧化焦磷酸鈣、假性痛風、軟骨鈣化、關節液分析