

Frequency and determinants of calcium pyrophosphate dihydrate deposition in patients with rheumatoid arthritis: A radiologic study

Romatoid artritte kalsiyum pirofosfat dihidrat birikim sıklığı ve ilişkili faktörler: Radyolojik bir çalışma

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Abstract

Objective: Previous joint injury predisposes to calcium pyrophosphate dihydrate deposition (CPPD). In this study, we aimed to identify the frequency and associated factors of radiographic CPPD signs in cases of rheumatoid arthritis (RA).

Methods: Adult patients with RA who were referred to our tertiary rheumatology department between January 2023 and December 2024 were included. Patients with secondary rheumatologic diseases and conditions predisposing to CPPD were excluded. Chondrocalcinosis, scapholunate advanced collapse, scaphoid-trapezium-trapezoid joint collapse, and hook-like osteophytes on hand X-rays were defined as the signs of CPPD. Radiographs were read by two blinded rheumatologists.

Results: We included a total of 1,318 patients; 83% of them were female. The mean age was 55.2 years, and the mean disease duration was 8.6 years. Rheumatoid factor and anti-cyclic citrullinated peptide (CCP) positivity were 56.2% and 52.7%, respectively. 95.5% of the patients had RA-type erosive changes. We found the frequency of CPPD as 10.5% (n=139). The most common CPPD sign was chondrocalcinosis of distal interphalangeal joints (n=70), and hook-like osteophytes were the second (n=48). The mean age ($p<0.001$), disease duration ($p=0.002$), anti-CCP negativity ($p<0.001$), and RA-type serious joint involvement ($p=0.008$) were significantly higher in the CPPD+ group. In multivariate analysis, age ($p<0.001$), disease duration ($p=0.007$), and anti-CCP negativity ($p=0.002$) were the independent predictive factors for CPPD.

Conclusion: Our findings align with prior literature suggesting that joint damage in RA may predispose patients to CPPD. Moreover, CPPD is a clinical entity that should be kept in mind in the management of RA.

Keywords: Chondrocalcinosis, crystal arthropathies, hand, rheumatoid arthritis, risk factors

Özet

Amaç: Önceki eklem hasarı, kalsiyum pirofosfat dihidrat birikimine (CPPD) yatkınlık yaratır. Bu çalışmada eroziv bir eklem hastalığına sahip romatoid artrit (RA) olgularında radyografik CPPD bulgularının sıklığını ve ilişkili faktörleri tanımlamayı amaçladık.

Yöntem: Ocak 2023 ile Aralık 2024 tarihleri arasında üçüncü basamak romatoloji kliniğimize başvuran erişkin RA hastaları çalışmaya dahil edildi. Sekonder romatolojik hastalıklara ve CPPD hastalığı için predispozan hastalıklara sahip olan olgular çalışmadan dışlandı. Anteroposterior el radyografilerinde kondrokalsinozis, skafo-lunat eklemdede kollaps ve skafoide-trapezyum-trapezoid eklemdede kollaps ve kanca benzeri osteofitler "CPPD bulguları" olarak tanımlandı. Röntgenler, hastalara kör iki romatolog tarafından değerlendirildi.

Bulgular: Çalışmaya toplam 1.318 hasta alındı ve bunların %83'ü kadındı. Ortalama yaş 55,2 yıl, ortalama hastalık süresi ise 8,6 yıldır. Romatoid faktör ve anti-CCP pozitifliği sırasıyla %56,2 ve %52,7 idi. Hastaların %95,5'inde RA'ya özgü eroziv değişiklikler mevcuttu. Çalışma grubunda CPPD sıklığı %10,5 idi (n=139). En sık görülen CPPD bulgusu distal interfalangeal eklemlerde kondrokalsinozis (n=70) olup, ikinci en sık bulgu kanca benzeri osteofitlerdi (n=48). Yaşı ($p<0,001$), hastalık süresi ($p=0,002$), anti-siklik sitrülüne peptit (CCP) negatifliği ($p<0,001$) ve RA tipi ciddi eklem tutulumu ($p=0,008$) CPPD+ grupta anlamlı olarak daha yüksekti. Çok değişkenli analizde ise yaş ($p<0,001$), hastalık süresi ($p=0,007$) ve anti-CCP negatifliğini ($p=0,002$) RA olgularında için bağımsız prediktif faktörler olarak saptadık.

Sonuç: Bulgularımız, RA olgularındaki eklem hasarının hastaları CPPD birikimine yatkın hale getirebileceğini öne süren önceki literatürle uyumludur. Ayrıca, CPPD, RA yönetiminde akılda tutulması gereken bir klinik antitedir.

Anahtar Kelimeler: Kondrokalsinozis, kristal artropatileri, el, romatoid artrit, risk faktörleri

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Introduction

Calcium pyrophosphate dihydrate deposition (CPPD) disease is a crystal arthropathy that is caused by CPP crystals. The prevalence of CPPD is 4-7% in Europe and the United States, which usually affects the elderly population, especially those over 60 years old. Although the pathogenesis of CPPD remains unclear, pre-existing cartilage injury is an important predisposing factor. As a result, CPPD disease often coexists with osteoarthritis (OA). The most common cause of CPPD disease is idiopathic, but some metabolic disorders are associated with it.^[1]

The clinical presentation of CPPD varies widely, including forms such as asymptomatic chondrocalcinosis (CC), acute arthritis, chronic arthritis, and tumoral deposition.^[2,3] The knee and shoulder are the most commonly affected joints in CPPD disease, but small joints such as metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints can also be involved.^[2] Moreover, erosive arthritis may develop during the course of CPPD disease.^[4] Despite the fact that a definitive diagnosis is based on determining the crystals in synovial fluid (SF), radiographic CC supports the diagnosis of CPPD disease.^[5]

Rheumatoid arthritis (RA) is a multisystem inflammatory disease that affects peripheral synovial joints. The prevalence of RA is 0.5-1%, and it has a higher occurrence in females. This condition is one of the most frequently encountered rheumatic diseases in routine clinical practice. Both innate and adaptive immune responses drive the pathogenesis of RA; chronic synovitis leads to cartilage and bone erosions in the natural course of RA.^[6] RA typically presents insidiously with initial involvement of the small joints of the hands, such as MCP and PIP, and large joint involvement, such as the knee or hip, is a finding of later stages of RA. Up to 90% of RA cases have hand involvement during the disease course.^[7,8]

RA may create a conducive environment for the development of CPPD disease due to its erosive effects on bone and cartilage tissues. A national database study from the United States demonstrated a positive association between RA and CPPD.^[9] However, the frequency and risk factors of hand CPPD in patients with RA remain unclear. To date, no studies have addressed this topic in the medical literature. In this study, we aimed to determine the frequency and associated factors of radiographic CPPD signs in hand joints of RA patients.

Materials and Methods

Patient Selection

We surveyed patients with RA who were referred to the outpatient clinic of our tertiary rheumatology department between January 2023 and December 2024. Electronic

medical records were reviewed retrospectively. Demographic, laboratory, and treatment data were documented. The inclusion criteria were: being aged ≥ 18 years, fulfilling the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) RA classification criteria,^[10] and having an anteroposterior hand X-ray in the past year. The exclusion criteria were diagnosed with familial CPPD disease, having a bone fracture history at hand or wrist joints, having another rheumatic disease causing chronic synovitis at hand joints, such as psoriatic arthritis,^[11] Sjögren's syndrome,^[12] systemic sclerosis,^[13] and having CPPD-associated metabolic disorders such as hyperparathyroidism, hemochromatosis, hypomagnesemia, Gitelman's disease, Bartter's disease, and, gout.^[1,14] Patients with erosive OA and hand OA^[15] were excluded from the study because of their strong association with CPPD disease. Patients with chronic kidney disease (CKD) were excluded because CKD is associated with CPPD.^[9]

Assessments

Rheumatoid arthritis-joint involvement (RJI) was defined as the presence of erosion or joint space narrowing (JSN) in any joint, as assessed using the modified sharp scoring (MSS) system,^[16] "serious joint involvement (SJI) was characterized by an erosion score of ≥ 3 points or a JSN score of ≥ 4 points in any joint, as assessed by the MSS". The EULAR definition was employed to characterize the typical joint erosion of RA (as a cortical break).^[17]

CC (which is the most common sign of CPPD disease), scapholunate advanced collapse/radiocarpal joint CC, scaphoid-trapezium-trapezoid joint collapse, and hook-like osteophytes on anteroposterior hand X-rays were accepted as signs of CPPD disease.^[18] Radiological evaluations were independently conducted by two experienced rheumatologists (MP and GK), who were blinded to clinical data. In the event of disagreement between readers, the X-rays were re-evaluated, and a final consensus decision was reached through full agreement.

Rheumatoid factor (RF) was measured using a nephelometric method, and serum levels ≥ 14 IU/mL were considered positive. Anti-cyclic citrullinated peptide (CCP) antibody-2 IgG levels were assessed using an enzyme-linked immunosorbent assay, with values of ≥ 5 U/mL classified as positive. CKD was defined as a glomerular filtration rate below 60 mL/min/1.73 m², persisting for at least three months.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics version 22.0 (Chicago, IL). Data were presented as counts, frequencies, and percentages. Categorical variables and their associations were evaluated using the chi-square test and Fisher's exact test. Depending on the data distribution, group

comparisons were carried out using either the Mann-Whitney U test or the Independent Samples t-test. Multivariate analysis was employed to estimate the probabilities of the dependent variable and to classify outcomes based on these probability estimates. A 95% confidence interval (CI) was used for all analyses, and a p-value of less than 0.05 was considered statistically significant.

The study received ethical approval from the Ethics Committee of Hatay Mustafa Kemal University, where the study was conducted (approval date: 06.08.2024, protocol number: 08, decision number: 46).

Results

We consecutively reviewed 1,402 patients and included a total of 1,318 patients in our study. Figure 1 shows the data on the exclusion of the study population. Eighty-three percent of them were female, and the mean age was 55.2 years. The mean disease duration was 8.6 years. The frequency of smoking history (active or ex) was 32.2%. RF positivity was 56.2%, and anti-CCP positivity was 52.7%. The 95.5% of patients had RJI, and 25.8% had SJI. The 30.2% (n=399) of patients were being treated with biologic or targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs). The frequency of CPPD was found to be 10.5% (n=139). Table 1 presents the characteristics of the study population.

The overall number of CPPD lesions was 201. The most common CPPD sign was the CC of distal interphalangeal (DIP) joints (n=70), and drooping osteophytes were the second most common (n=48). We detected CC at multiple joint levels, such

as the wrist, MCP, PIP, and DIP joints. Table 2 presents the detailed radiographic analysis of hand CPPD. Figure 2 and Figure 3 show examples of hand CPPD in RA cases.

The CPPD+ group had a significantly higher mean age ($p<0.001$), longer disease duration ($p=0.002$), more frequent anti-CCP negativity ($p<0.001$), and more cases of SJI ($p=0.008$) compared to the CPPD- group. A multivariate analysis model (including age, disease duration, anti-CCP, and SJI) showed that age [odds ratio (OR)=1.89; 95% CI: 1.167-3.211; $p<0.001$], disease duration (OR=2.24; 95% CI: 1.418-3.612; $p=0.007$), and anti-CCP negativity (OR=2.13; 95% CI: 1.335-3.409; $p=0.002$) were the independent predictive factors of CPPD. Table 3 presents the comparison of two groups according to CPPD status.

Discussion

In this radiographic study, we first defined the frequency, associated factors, and radiographic signs of hand CPPD in patients with RA in medical literature. We found 10.5% of RA cases had CPPD in hand joints. Age, disease duration, and anti-CCP negativity were the independent predictive factors of CPPD. According to our results, advanced age, long disease duration, anti-CCP negativity, and SJI were associated with CPPD in RA cases. Our findings are consistent with the pathogenesis of CPPD, as prolonged disease duration and SJI are likely to lead to greater joint damage. Our findings align with prior literature suggesting that joint damage in RA may predispose patients to CPPD deposition.

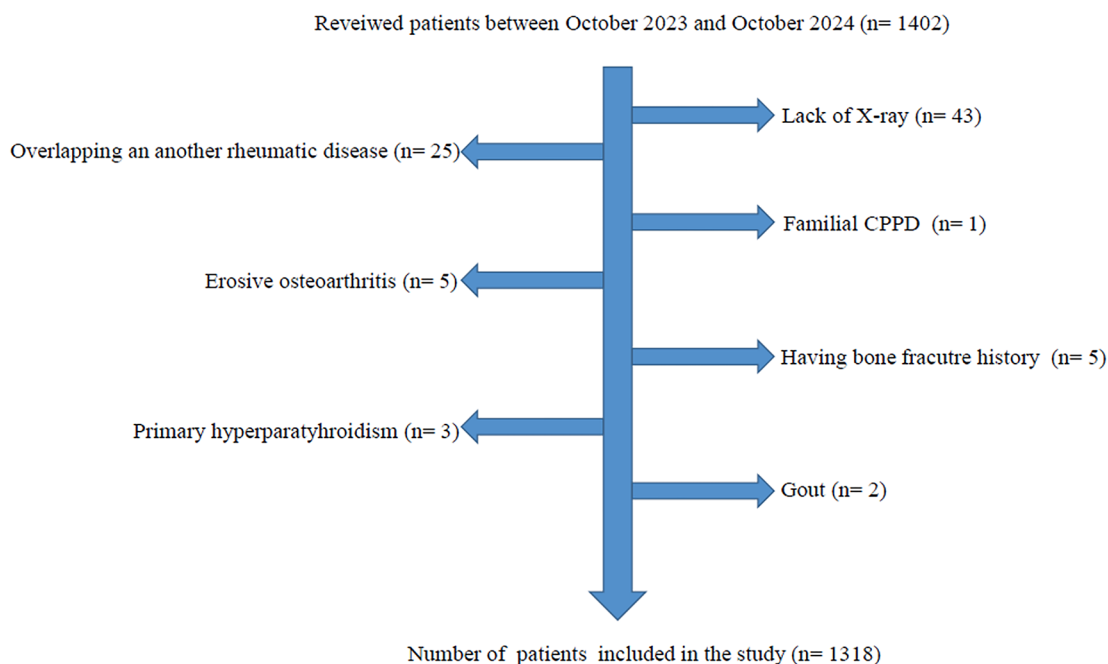


Figure 1. Flowchart of the study representing the criteria and number of patients from initial retrieval to the final study cohort
CPPD: Calcium pyrophosphate deposition

Table 1. Demographic, laboratory, and treatment characteristics of study population

Total patient, n	1,318
Age, mean $\pm$ SD, years	55.2 $\pm$ 12.6
Disease duration, mean $\pm$ SD, years	8.6 $\pm$ 7.5
Female sex, n (%)	1093 (83)
Male sex, n (%)	225 (17)
Smoking, n (%)	425 (32.2)
Hypertension, n (%)	390 (29.6)
Diabetes mellitus, n (%)	190 (14.4)
Coronary artery disease, n (%)	124 (9.4)
RF positivity, n (%)	741 (56.2)
Anti-CCP positivity, n (%)	695 (52.7)
b/tsDMARD use, n (%)	399 (30.2)
RJI, n (%)	1259 (95.5)
SJI, n (%)	341 (25.8)
CPPD, n (%)	139 (10.5)

Anti-CCP: Anti-cyclic citrullinated peptide, b/tsDMARD: Biologic/targeted synthetic disease modifying anti-rheumatic drugs, CPPD: Calcium pyrophosphate deposition, RF: Rheumatoid factor, RJI: Rheumatoid arthritis-type joint involvement, SD: Standard deviation, SJI: Serious joint involvement

Paalanen et al.^[19] found the prevalence of radiographic CPPD to be 3.2% in 435 early seronegative RA patients. All patients with CPPD had CC at triangular cartilage. This study did not report CPPD findings other than triangular CC, and none of the patients with CPPD had typical RA-like erosions. The authors suggested that CPPD disease can mimic seronegative RA. In our cohort, the mean disease duration was 8.6 years, and 95.5% of patients had RJI, so clinical mimicry of CPPD was not observed. Sabchysyn et al.^[20] reported 21 patients with overlap syndrome between RA and CPPD, which was diagnosed by CC on X-rays. The authors reported that RA usually precedes CPPD disease and that CPPD disease can be a complication of established RA.

Gerster et al.^[21] conducted a study involving 93 patients with RA (the mean age and disease duration were 64.5 years and 12 years, respectively), and investigated CPPD by SF analysis of knee joints, finding a prevalence of 25.8%. Patients with CPPD had more joint prostheses than those in the CPPD-negative group, but there was no significant difference in disease duration between the groups. Theiler et al.^[22] evaluated CC in the knees of RA patients using SF analysis via the cytopspin technique. They reported a CPPD prevalence of 17.7%, with age identified as an independent predictive factor ($p < 0.001$). Disease activity scores and serologic markers were not associated with CPPD. Galozzi et al.^[23] investigated the frequency of CPP crystals in the SF of wrist and finger joints and reported prevalence rates 85.7%, 19.3%, 13.9%, and 0% in patients with RA, OA, psoriatic arthritis, and gout, respectively. The wrist was the most common site for CCP crystals, followed by MCP, PIP, and DIP joints. The higher frequency of CPP crystals in RA than OA, may suggest a potential link between the severity of

Table 2. Radiographic analysis of CPPD findings

Total CPPD lesion count, n	203
-Hook-like osteophytes, n (%)	48 (23.9)
-Scapholunate advanced collapse/RC joint CC, n (%)	11 (5.4)
-Scaphoid-trapezium-trapezoid joint collapse, n (%)	6 (3)
-First carpometacarpal joint CC, n (%)	13 (6.4)
-DIP joint CC, n (%)	70 (34.9)
-MCP joint CC, n (%)	33 (16.4)
-PIP joint CC, n (%)	17 (8.5)
-Triangular cartilage CC, n (%)	3 (1.5)
Hook-like osteophytes, n (%)	
-2. MCP joint	10 (20.8)
-3. MCP joint	27 (56.3)
-4. MCP joint	5 (10.4)
-5. MCP joint	6 (12.5)
CC in DIP joints, n (%)	
-2. DIP joint	35 (50)
-3. DIP joint	20 (28.5)
-4. DIP joint	10 (14.3)
-5. DIP joint	5 (7.2)
CC in MCP joints, n (%)	
-1. MCP joint	1 (3)
-2. MCP joint	9 (27.3)
-3. MCP joint	10 (30.3)
-4. MCP joint	7 (21.2)
-5. MCP joint	6 (18.2)
CC in PIP joints, n (%)	
-2. PIP joint	2 (11.8)
-3. PIP joint	11 (64.7)
-4. PIP joint	4 (23.5)
-5. PIP joint	0

CC: Chondrocalcinosis, CPPD: Calcium pyrophosphate deposition, DIP: Distal interphalangeal, MCP: Metacarpophalangeal, PIP: Proximal interphalangeal, RC: Radiocarpal

**Figure 2.** A 66 years old female patients with rheumatoid arthritis; erosion in the styloid process of ulna, and chondrocalcinosis in the second distal interphalangeal joint were shown with red arrows

inflammation and CPPD. Oliviero et al.^[24] also analyzed the SF of patients with inflammatory joint disease, including 326 patients with RA (the mean age and disease duration were 58.8 years and seven years, respectively). They found the frequency of CPP crystals was 8.2% in patients with RA, and the CPP

crystal-positive group was significantly older ($p<0.001$) than the CPP crystal-negative group, but there was no difference in terms of disease duration.

Advanced age has been consistently identified as a significant risk factor for CPPD disease, a finding that is further corroborated by the results of our study.^[25] We defined the disease duration as an independent predictive factor for CPPD disease, which may result from progressive cartilage and bone destruction during the course of RA. Anti-CCP is a commonly utilized test in clinical practice for the diagnosis of RA; it is included in the 2010 ACR/EULAR RA classification criteria.^[10] The presence of anti-CCP antibodies is also observed in several immune-mediated inflammatory diseases, such as connective tissue diseases, psoriatic arthritis, Crohn's disease, and COVID-19, where citrullination processes are involved.^[26] We defined the anti-CCP negativity as an independent predictive factor for CPPD. Therefore, we could hypothesize the absence of citrullination processes in the pathogenesis of CPPD. Krekeler et al.^[27] also supported our results, finding that seronegative RA patients had a higher prevalence of CC compared to seropositive patients.

Another important issue is the difference in treatment strategies between RA and CPPD disease. The EULAR recommends conventional synthetic or biologic/targeted

synthetic DMARDs in patients with RA, but none of the DMARDs are currently indicated for the treatment of CPPD disease. Moreover, colchicine, which is recommended for the treatment of crystal arthritis but not for RA, may be a beneficial option for patients with RA who have overlapping CPPD.^[28,29] Furthermore, CPPD may present as acute or chronic arthritis and lead to overtreatment in patients with RA. In our cases, there was no notable statistical difference in b/tsDMARD use between the CPPD (+) and (-) groups ($p=0.52$).

This study was a radiographic investigation, in which we identified the radiographic signs of CPPD rather than diagnosing CPPD disease in RA patients. We could not apply 'The 2023 ACR/EULAR classification criteria for CPPD disease' to our study population because that criteria includes the RA as an absolute exclusion criteria.^[30] Additionally, our study population had low positivity rates of RF and anti-CCP antibodies according to the medical literature. This may be due to varying positivity rates of these autoantibodies among different populations with RA. A recent study from Türkiye reported RF and anti-CCP positivity rates of 40.3% and 35.6%, respectively, in patients with newly diagnosed RA.^[31,32] We did not consider a diagnostic inaccuracy among RA patients because 95% of them had RJI.

Study Limitations

Despite unique results, our study had some limitations, such as a retrospective design, lack of a healthy control group, intra- and inter-observer variability, and the low sensitivity of conventional radiography, which may fail to detect CC, particularly in small joints.^[33] Furthermore, hook-like osteophytes are not specific to RA and can be observed in patients with RA in remission.^[34] Some of the patients with SJI had joint ankylosis, so we could not detect CC in these patients. Moreover, the absence of CC does not exclude the CPPD diagnosis.^[5] Therefore, we suggest that the prevalence of hand CPPD in patients with RA may be higher than observed in our study. Ultrasound is more sensitive and less specific than conventional radiography; however, both imaging modalities demonstrate good diagnostic accuracy for CPPD.^[35] Another important limitation is that primary CPPD can present with erosive arthritis even in the absence of RA.^[2] Moreover, the CPPD may mimic a pseudo-RA pattern.^[36] Although CPPD-related erosions are not clearly defined radiologically and 95% of our RA cases exhibited RA-type joint involvement, diagnostic challenges may still have occurred.

Conclusion

In conclusion, this is the first study to investigate radiographic hand CPPD in patients with RA. We identified the frequency of CPPD as 10.5%, with age, disease duration, and anti-CCP negativity emerging as independent predictive

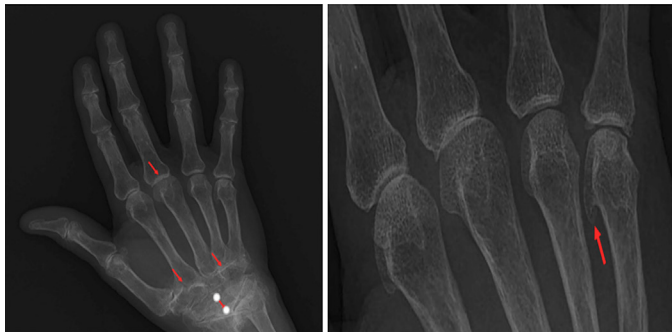


Figure 3. A 58 years old female patients with rheumatoid arthritis; multiple joint space narrowing in wrist joints, and hook-like osteophytes in the fifth metacarpophalangeal joint were shown with red arrows

Table 3. Comparison of RA patients according to the CPPD status

Variable	CPPD+ group	CPPD- group	p-value
Age, mean $\pm$ SD, years	64.5 $\pm$ 10.1	54.1 $\pm$ 12.5	<0.001
Female sex, %	83.5	82.9	0.86
Disease duration, mean $\pm$ SD, years	11.1 $\pm$ 9.5	8.3 $\pm$ 7.1	0.002
Smoking history, %	28.1	32.7	0.26
RF positivity, %	48.9	57.1	0.06
Anti-CCP positivity, %	38.1	54.5	<0.001
Serious joint involvement, %	35.3	24.8	0.008
b/tsDMARD use, %	28.1	30.7	0.52

Anti-CCP: Anti-cyclic citrullinated peptide antibody-2 IgG, b/tsDMARD: Biologic or targeted synthetic disease modifying anti-rheumatic drugs, CPPD: Calcium pyrophosphate deposition, RA: Rheumatoid arthritis, RF: Rheumatoid factor, SD: Standard deviation

factors. Additionally, we were the first to report radiographic signs of CPPD beyond CC. Rheumatologists should consider the possibility of CPPD in RA patients, particularly in the presence of the identified risk factors, to ensure optimal disease management. Prospective studies are needed to clarify the underlying mechanisms of this association and to enhance therapeutic strategies for affected individuals.

Ethics

Ethics Committee Approval: The study received ethical approval from the Ethics Committee of Hatay Mustafa Kemal University, where the study was conducted (approval date: 06.08.2024, protocol number: 08, decision number: 46).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.P., G.K., Concept: M.P., G.K., Design: M.P., G.K., Data Collection and Processing: M.P., G.K., Analysis or Interpretation: M.P., G.K., Literature Search: M.P., G.K., Writing: M.P., G.K.

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