Clinical features and risk of recurrence of acute calcium pyrophosphate crystal arthritis

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Abstract

Objective

It is unclear whether attack recurrence rates are similar between acute calcium pyrophosphate (CPP) crystal arthritis and gout. This study compared the clinical features and recurrence rates of both conditions.

Methods

In this retrospective study, we reviewed 106 patients with acute CPP crystal arthritis (based on the presence of CPP crystals and/or chondrocalcinosis) and 173 patients with gout (based on the presence of monosodium urate crystals). We analysed clinical variables and compared them between the two conditions. We identified factors associated with the recurrence of acute CPP crystal arthritis.

Results

Patients with acute CPP crystal arthritis were older (76.5 vs. 62 years, p<0.001) and female (69.8% vs. 6.9%, p<0.001); they had a lower body mass index (22.3 vs. 23.7, p=0.002), lower renal insufficiency rate (27.4% vs. 41.6%, p=0.016), and higher rate of preceding infection (22.6% vs. 11.0%, p=0.009) than those with acute gout. Recurrence rates were similar between the groups (19.1% vs. 22.9%, p=0.562). Use of proton pump inhibitors (PPIs) [hazard ratio (HR), 5.625; 95% CI, 1.672–18.925; p=0.005] and warfarin (HR, 7.301; 95% CI, 1.930–27.622; p=0.003) or exposure to chemotherapy (HR, 5.663; 95% CI, 1.180–27.169; p=0.03) were associated with acute CPP crystal arthritis recurrence.

Conclusion

Acute CPP crystal arthritis was more common than acute gout in older women with preserved renal function. Physicians should be aware of the association between recurrence and PPI, warfarin, or chemotherapy use in these patients.

Key words

acute CPP crystal arthritis, CPPD, gout, recurrence

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Received on January 26, 2018; accepted in revised form on May 29, 2018.

Funding: this work was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (grant no. HI15C3117).

Competing interests: none declared.

Introduction

Calcium pyrophosphate deposition (CPPD) is frequently asymptomatic but can present as a form of arthritis called CPPD disease. Clinical phenotypes of CPPD disease include acute CPP crystal arthritis, CPPD with osteoarthritis, or chronic CPP crystal inflammatory arthritis (1). Acute CPP crystal arthritis, termed as pseudogout, is the most widely recognised form of CPPD disease (2). Patients with acute CPP crystal arthritis typically present with acute painful mono- or oligoarthritis resembling an acute gout attack.

Acute gout attacks manifest as acute arthritis episodes with a predilection for the first metatarsophalangeal (MTP) joint; followed in order of frequency by the mid-foot and ankles. In contrast, acute CPP crystal arthritis typically involves large joints such as the knee or wrist, with less common involvement of the hand or shoulder, and only rarely affecting the first MTP joint (3, 4). Reports have shown that patients with acute CPP crystal arthritis are older than those with acute gouty arthritis (4, 5). Ultrasound has been shown to be at least as accurate as synovial fluid microscopic analysis and more sensitivity than radiography for CPPD diagnosis (6). In addition, the double-contour sign on ultrasound examinations is a specific finding of gout (7). Thus, ultrasound may help to diagnose acute crystal arthropathy. However, the clinical features of acute CPP crystal arthritis are often indistinguishable from those of acute gouty arthritis. Moreover, research has focused on the differences in the underlying conditions and predisposing factors between acute CPP crystal arthritis and acute gouty arthritis is very limited. Furthermore, it is unknown whether recurrences are similarly frequent between the two conditions. Therefore, in this study, we compared clinical features of acute CPP crystal arthritis to those of acute gouty arthritis and identified clinical factors associated with the recurrence of acute CPP crystal arthritis during the follow-up period.

Methods

Study population

In this retrospective cohort study, we reviewed the electronic medical records of patients diagnosed with acute CPP crystal arthritis and those diagnosed with acute gouty arthritis at the Asan Medical Center, in the Ulsan University College of Medicine, in Seoul (Korea) between January 2000 and December 2016. We included data from patients with acute arthritis who underwent joint fluid aspiration and who fulfilled the diagnostic criteria for either gout or acute CPP crystal arthritis. We excluded patients <18 years of age. Diagnosis of acute CPP crystal arthritis was based on the presence of clinical acute synovitis features and the presence of CPP crystals on polarising microscopy of the joint fluid (definite CPPD disease); the presence of punctate and linear calcification on radiographs in the affected joints (probable CPPD disease); or the acute arthritis of the knee, wrist, shoulder, hip or ankle (possible CPPD disease) (8). The diagnosis of gout was made during an acute arthritis attack based on the presence of needle-shaped monosodium urate (MSU) crystals in the joint fluid. We collected the following data from medical records: (1) Demographic information including age, gender, and body mass index (BMI, kg/m^2); (2) Information regarding accompanying medical conditions such as hypertension, diabetes mellitus, renal insufficiency (estimated glomerular filtration rate <60 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration equation), coronary artery disease (CAD), active tuberculosis, stroke, atrial fibrillation (AF), cancer and hypothyroidism; (3) Predisposing factors, such as surgery, infection, trauma, and medication [furosemide, thiazide, aspirin, warfarin, proton pump inhibitor (PPI) or chemotherapy, and use of colchicine or non-steroidal anti-inflammatory drugs (NSAIDs) after initial attack]; (4) Number and distribution of involved joints; and (5) Laboratory data including white blood cell (WBC) and neutrophil counts, serum C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), and serum urate, corrected calcium and phosphate levels. We also analysed the results of joint fluid analysis, including the WBC counts. The diagnosis of recurrent acute CPP

crystal arthritis was based on clinical features of acute arthritis with definite, probable, or possible CPPD disease (with or without CPP crystals in the joint fluid) (8). The diagnosis of recurrent gout attack was made based on the 2015 Gout Classification Criteria (7). In order to reduce potential bias, two investigators independently assessed the diagnosis of recurrent attacks.

The Institutional Review Board of Asan Medical Center, Seoul, Korea approved this study (IRB no. 2017-0854). The requirement for informed consent was waived because of the retrospective nature of the study.

Statistical analysis

We compared clinical features between patients with acute CPP crystal arthritis and acute gouty arthritis. *p*-values <0.05 were considered to be statistically significant. We used the chi-square test and Fisher's exact test to compare categorical data. For continuous variables, we used the Student's *t*-test if the data were normally distributed. We analysed corrected calcium values using the Student's *t*-test because they were normally distributed. We used the Mann-Whitney U-test to analyse other continuous variables, which showed non-parametric distributions. We excluded missing data from the analysis.

We performed Cox regression analyses with backward elimination procedures to identify risk factors for recurrence of acute CPP crystal arthritis. Variables with a *p*-value <0.2 on univariate analyses were selected for multivariate analyses. We used the SPSS 20.0 software (SPSS, Chicago, IL, USA) for all statistical analyses.

Results

Comparison between acute CPP crystal arthritis and acute gouty arthritis

In total, we identified 106 patients with acute CPP crystal arthritis (69 with definite CPPD disease, 32 with probable CPPD disease, and 5 with possible CPPD disease) and 173 with acute gouty arthritis and included their data in the study. Table I shows the baseline clinical characteristics and laboratory findings for patients with acute CPP crystal arthritis and acute gouty arthritis. The mean age of the patients with acute CPP crystal arthritis was higher than that for patients with acute gouty arthritis (76.5; IQR, 70.8–82.3 *vs*. 62; IQR, 53–71; $p<0.001$). In addition, patients with acute CPP crystal arthritis were predominantly women and had a lower mean BMI than those with acute gouty arthritis. We found no significant differences in the presence of comorbidities, including hypertension, diabetes mellitus, CAD, tuberculosis, stroke, AF, cancer, or hypothyroidism, between

Table I. Comparison of the variables between patients with acute CPP crystal arthritis and those with acute gouty arthritis.

	Acute CPP crystal arthritis (n=106)	Acute gouty Arthritis (n=173)	*p*-value
Age [years, median (IQR)]	76.5 (70.8–82.3)	62 (53–71)	<0.001
Women	74 (69.8)	12 (6.9)	<0.001
BMI [kg/m², median (IQR)] *	22.3 (20.5–25) (n = 93)	23.7 (22–26.7) (n = 153)	0.002
Comorbidities			
Hypertension	57 (53.8)	76 (43.9)	0.110
Diabetes mellitus	29 (27.4)	52 (30.1)	0.630
Renal insufficiency	29 (27.4)	72 (41.6)	0.016
CAD	11 (10.4)	19 (11)	0.874
Tuberculosis	0 (0)	6 (3.5)	0.086
Stroke	4 (3.8)	13 (7.5)	0.205
AF	11 (10.4)	23 (13.3)	0.470
Cancer	29 (27.4)	35 (20.2)	0.169
Hypothyroidism	4 (3.8)	2 (1.2)	0.205
Predisposing factors			
Surgery	12 (11.3)	25 (14.5)	0.454
Infection	24 (22.6)	19 (11)	0.009
Trauma	11 (10.4)	8 (4.6)	0.064
Drug uses			
Furosemide	10 (9.4)	27 (15.6)	0.140
Thiazide	5 (4.7)	9 (5.2)	0.857
Aspirin	13 (12.3)	18 (10.4)	0.631
Warfarin	5 (4.7)	17 (9.8)	0.124
PPI	13 (12.3)	16 (9.2)	0.423
Chemotherapy	8 (7.5)	8 (4.6)	0.308
Articular involvement			0.712
Monoarticular	72 (67.9)	112 (64.7)	
Oligoarticular	31 (29.2)	53 (30.6)	
Polyarticular	3 (2.8)	8 (4.6)	
Foot	4 (3.8)	30 (17.3)	0.001
Ankle	8 (7.5)	50 (28.9)	<0.001
Knee	101 (95.3)	134 (77.5)	<0.001
Wrist	8 (7.5)	13 (7.5)	0.992
Elbow	4 (3.8)	10 (5.8)	0.456
Hand	3 (2.8)	8 (4.6)	0.542
Shoulder	3 (2.8)	0 (0)	0.054
Fever	56 (52.8)	76 (43.9)	0.148
Joint fluid analysis			
WBC [/μL, median (IQR)]	22,200 (12,340–47,700)	25,000 (9,600–56,800)	0.810
Neutrophil [/μL, median (IQR)]	19,360 (9,859–43,530)	23,850 (8,186–50,892)	0.426
Blood laboratory data			
WBC [/μL, median (IQR)]	9,500 (7200–12,000)	9,600 (7,500–11,800)	0.667
Neutrophil [/μL, median (IQR)]	7,100 (4361–9141)	6,894 (5,178–9,026)	0.805
CRP [mg/dl, median (IQR)]*	9.7 (5.3–16.4) (n=96)	9 (3.7–14.3)	0.153
ESR [mm/hr, median (IQR)]*	67 (50–99) (n=79)	64 (34–90.5) (n=129)	0.096
GFR [ml/min/1.73m², median (IQR)]	81.2 (57.8-92)	69.6 (36.2-90.9)	0.005
Uric acid [mg/dL, median (IQR)]*	3.9 (2.8–5.3) (n=94)	7.6 (5.6–9.1)	<0.001
Corrected calcium [mg/dL, mean (SD)]*	9.4 (0.5) (n=94)	9.3 (0.5)	0.104
Phosphate [mg/dL, median (IQR)]*	2.9 (2.4–3.4) (n=58)	3.2 (2.8–3.9) (n=146)	0.001

*Missing values were excluded from analysis. CPP: calcium pyrophosphate; IQR: interquartile range; CAD: coronary artery disease; AF, atrial fibrillation; PPI: proton pump inhibitor; WBC: white blood cell; ESR: erythrocyte sedimentation rate; GFR: glomerular filtration rate.

Table II. Outcomes of acute CPP crystal arthritis and acute gouty arthritis.

	Acute CPP crystal arthritis (n=94)	Acute gouty arthritis (n=70)	*p*-value
Follow-up duration [weeks, median (IQR)]	46 (16–95.5)	50 (9.5–134)	0.868
Time to recurrence [weeks, median (IQR)]	17.5 (9.8–35.8)	7 (5.3–46)	0.207
Recurrence rate	18 (19.1)	16 (22.9)	0.562

CPP: calcium pyrophosphate; IQR: interquartile range.

Table III. Univariate analysis of variables associated with recurrence of acute CPP crystal arthritis.

	HR	95% CI	*p*-value
Age	0.781	0.625–0.975	0.029
BMI* (n = 82)	0.919	0.793–1.065	0.261
Women	0.636	0.235–1.724	0.374
Hypertension	0.601	0.235–1.534	0.287
Diabetes mellitus	0.895	0.318–2.516	0.833
Renal insufficiency	1.05	0.302–3.657	0.938
Stroke	0.045	0–335.380	0.496
Hypothyroidism	0.048	0–18445.403	0.643
Cancer	0.910	0.296–2.801	0.869
History of joint replacement	0.037	0–28.486	0.332
History of intra-articular injection	0.476	0.061–3.722	0.479
Use of warfarin	4.706	1.348–16.424	0.015
Use of PPI	3.740	1.204–11.615	0.023
Use of furosemide	1.396	0.459–4.246	0.557
Use of thiazide	0.048	0–40869.318	0.709
Use of bisphosphonate	1.668	0.221–12.613	0.620
Use of aspirin	0.784	0.179–3.438	0.746
Chemotherapy	3.367	0.757–14.981	0.111
Use of colchicine	1.741	0.396–7.648	0.463
Use of NSAIDs	1.128	0.442–2.881	0.801

*Missing value was excluded form analysis. CPP: calcium pyrophosphate; HR: hazard ratio; PPI: proton pump inhibitor; NSAIDs: non-steroidal anti-inflammatory drugs.

Table IV. Multivariate analysis of variables associated with recurrence of acute CPP crystal arthritis.

	HR	95% CI	*p*-value
PPI	5.625	1.672–18.925	0.005
Chemotherapy	5.663	1.180–27.169	0.030
Warfarin	7.301	1.930–27.622	0.003

HR: hazard ratio; PPI: proton pump inhibitor.

the two groups. However, patients with acute CPP crystal arthritis were less likely to have renal insufficiency than those with acute gouty arthritis (29/106, 27.4% *vs*. 72/173, 41.6%; p=0.016). In addition, the frequency of preceding infection was significantly higher in patients with acute CPP crystal arthritis than in those with acute gouty arthritis (24/106, 22.6% *vs*. 19/173, 11.0%; p=0.009). Although the number of affected joints was not different, the affected sites were remarkably different between the two groups. The knee joint was more frequently involved in acute CPP crystal arthritis than in acute gouty arthritis. In contrast, foot and/or ankle joint involvement was more frequently observed in patients with acute gouty arthritis. We found that the leukocyte counts in the joint fluid and blood and serum CRP and ESR levels were not significantly different. The uric acid and phosphate levels in the blood were significantly lower in patients with acute CPP crystal arthritis than in those with acute gouty arthritis.

During the follow-up period, data were available for 94 of the 106 (88.7%) patients with acute CPP crystal arthritis and for 70 of the 173 (40.5%) patients with acute gouty arthritis (Table II). We excluded patients who were initiated on -urate lowering therapy because of its potential effect on the outcome of this study, including acute attack recurrences. The median follow-up durations were 46 weeks (IQR, 16–95.5) and 50 weeks (IQR, 9.5–134) in patients with acute CPP crystal arthritis and acute gouty arthritis, respectively. Recurrences occurred in 18 patients (19.1%) with acute CPP crystal arthritis and in 16 (22.9%) with acute gouty arthritis. This result was not significantly different between the two groups (p=0.562).

Clinical factors associated with acute CPP crystal arthritis recurrence

We performed Cox regression analysis to evaluate the clinical factors related to acute CPP crystal arthritis recurrence (Tables III and IV). Univariate analysis revealed that age, PPI use, and warfarin use were significantly associated with the development of recurrent acute CPP crystal arthritis (Table III). Based on the results of the univariate analysis, the variables that had p<0.2 were adjusted for our multivariate analysis. Multivariate analysis showed that PPI use [hazard ratio (HR), 5.625; 95% CI, 1.672–18.925; p=0.005] or warfarin use (HR, 7.301; 95% CI, 1.930–27.622; p=0.003) were associated with the risk of subsequent acute CPP crystal arthritis recurrence. In addition, exposure to chemotherapy resulted in a higher risk acute CPP crystal arthritis recurrence (HR, 5.663; 95% CI, 1.180–27.169; p=0.03) (Table IV).

Discussion

In this study, patients with acute CPP crystal arthritis were predominantly older women, had lower BMIs, and had a lower rate of renal insufficiency than those with acute gouty arthritis. In addition, the rate of preceding infection was significantly higher in patients with acute CPP crystal arthritis than in those with acute gouty arthritis; but inflammation, assessed by WBC counts in the blood and joint fluid, and the recurrence rate of acute CPP crys-

tal arthritis were similar between both conditions. Moreover, we identified that PPI or warfarin use and exposure to chemotherapy were associated with acute CPP crystal arthritis recurrence.

Patients with acute CPP crystal arthritis have been reported to be approximately 10 years older than those with acute gouty arthritis, and the female to male ratio of acute CPP crystal arthritis has been reported to be 75:25 (4). In our study, patients with acute CPP crystal arthritis were 14.5 years older than those with acute gouty arthritis and the female to male ratio was 70:30. In addition, we found that patients with acute CPP crystal arthritis had a lower incidence of renal insufficiency and lower serum uric acid levels than those with acute gouty arthritis. This finding is consistent with previous reports that higher uric acid levels are associated with a rapid decline in glomerular filtration rate and that renal impairment is associated with gout (9, 10). Interestingly, preceding infections were more frequently observed in patients with acute CPP crystal arthritis than in those with acute gouty arthritis (Table I). Infections observed in patients with acute CPP crystal arthritis include pneumonia (7/24, 29.5%), cholangitis (4/24, 16.7%), bacteraemia (4/24, 16.7%), acute pyelonephritis (3/24, 12.5%), vertebral osteomyelitis (2/24, 8.3%), cellulitis (2/24, 8.3%), herpes zoster virus infection (1/24, 4%), and infected prosthetic joint (1/24, 4%). Transient hypomagnesaemia associated with a critically ill status and/or antibiotic use may be the mechanisms through which preceding infections trigger acute CPP crystal arthritis (11, 12).

Leukocyte counts in the joint fluid have not been found to differ between patients with acute CPP crystal arthritis and those with acute gouty arthritis, but serum CRP levels have been shown to be significantly higher in the patients with acute CPP crystal arthritis than those with gouty arthritis(5). Our findings, however, showed that inflammatory activity assessed by the presence of fever and elevated serum CRP, ESR levels, and WBC counts in the blood or joint fluid, was not significantly different between the patients with acute CPP crystal arthritis and those with acute gouty arthritis. The production of IL-1β and IL-6 by monocytes and/or synoviocytes in response to the presence of MSU and CPP crystals has been found to be comparable (13, 14). These findings may explain the similar inflammatory activities in both groups of patients. Recurrent acute CPP crystal arthritis can lead to severe joint destruction and can progress rapidly (15). Studies have shown that hyperparathyroidism, osteoarthritis, osteoporosis, and hypomagnesemia are risk factors for CPPD (16). However, the factors associated with acute CPP crystal arthritis recurrences remain unclear. In our study, the use of PPI and the exposure to chemotherapy were associated with acute CPP crystal arthritis recurrence. Because CPP deposition is facilitated by hypomagnesaemia, and PPI and chemotherapy have both been linked to hypomagnesaemia (17-19), hypomagnesaemia may explain the risk of acute CPP crystal arthritis after exposure to PPI or chemotherapy.

At the same time, we identified warfarin use to be a risk factor for acute CPP crystal arthritis recurrence (Table IV; HR, 7.301; 95% CI, 1.930–27.622; p=0.003). Vitamin K-dependent proteins, such as the matrix Gla protein (MGP), function as inhibitors of extracellular matrix mineralisation (20). Warfarin prevents the activation of MGP in vascular smooth muscle cells, inducing vascular calcification. In addition, vascular and soft tissue calcifications have been associated with chondrocalcinosis (21). And, the incidence of extra-articular calcifications is increased in patients with CPPD disease (22). Thus, although the exact mechanisms are yet to be determined, warfarin-induced calcification may be responsible for the increased risk of acute CPP crystal arthritis recurrence.

We are aware of the limitations of our study. First, although ultrasound examination can help in the diagnosis of acute CPP crystal arthritis by confirming typical CPP crystal deposition findings in articular hyaline cartilage or fibrocartilage (6), the patients in our study did not undergo ultrasound examinations. Second, we determined acute CPP crystal arthritis recurrences retrospectively, based on medical records. Thus, we cannot exclude the possibility of undetected acute CPP crystal arthritis recurrences in the event that the patients did not visit the clinic. Third, our data sets had some missing data; but these missing data were largely pertaining to laboratory test results (CRP, ESR, uric acid, corrected calcium and phosphate) at initial attack and, therefore, do not affect acute CPP arthritis recurrence. Finally, only a small number of patients using warfarin or PPI, or undergoing chemotherapy were included in our analysis. Thus, further studies with larger numbers of subjects are required to confirm our findings.

In all, our results show that of the patients with acute CPP crystal arthritis are mostly older women with lower BMIs than the patients with gout. In addition, patients with acute CPP crystal arthritis usually have preserved renal function and a higher rate of preceding infections than patients with acute gouty arthritis. The recurrence rates for both the conditions are similar. And, the use of PPI and warfarin and chemotherapy are associated with subsequent risk of recurrence in patients with acute CPP crystal arthritis. Thus, careful follow-up should be considered for this group of patients.

References

1. ABHISHEK A, DOHERTY M: Update on calcium pyrophosphate deposition. *Clin Exp Rheumatol* 2016; 34: 32-8.
2. ZHANG W, DOHERTY M, BARDIN T *et al*.: European League Against Rheumatism recommendations for calcium pyrophosphate deposition. Part I: terminology and diagnosis. *Ann Rheum Dis* 2011; 70: 563-70.
3. GRAHAME R, SCOTT JT: Clinical survey of 354 patients with gout. *Ann Rheum Dis* 1970; 29: 461-8.
4. HO G, JR., DENUCCIO M: Gout and pseudogout in hospitalized patients. *Arch Intern Med* 1993; 153: 2787-90.
5. TAGOE CE, RAZA Y: Differences in acute phase reactants between gout and pseudogout. *Int J Clin Med* 2013; 4: 13-9.
6. FILIPPOU G, ADINOLFI A, CIMMINO MA *et al*.: Diagnostic accuracy of ultrasound, conventional radiography and synovial fluid analysis in the diagnosis of calcium pyrophosphate dihydrate crystal deposition disease. *Clin Exp Rheumatol* 2016; 34: 254-60.
7. NEOGI T, JANSEN TL, DALBETH N *et al*.: 2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2015; 74: 1789-98.

8. TERKELTAUB R: Calcium crystal disease: Calcium pyrophosphate dihydrate and basic calcium phosphate. *In* FIRESTEIN GS, BUDD RC, GABRIEL SE, MCINNES IB, O'DELL JR (Eds.): Kelly and Forestein's textbook of rheumatology, 10th edn, Philadelphia, PA, Elsevier 2017: 1645-65.
9. WANG W, BHOLE VM, KRISHNAN E: Chronic kidney disease as a risk factor for incident gout among men and women: retrospective cohort study using data from the Framingham Heart Study. *BMJ Open* 2015; 5: e006843.
10. TSAI CW, LIN SY, KUO CC, HUANG CC: Serum uric acid and progression of kidney disease: a longitudinal analysis and mini-review. *PLoS One* 2017; 12: e0170393.
11. RYZEN E, RUDE RK: Magnesium deficiency in bacteremic patients. *Arch Intern Med* 1988; 148: 249, 53.
12. KIM YW: Antimicrobial-induced electrolyte and acid-base disturbances. *Electrolyte Blood Press* 2007; 5: 111-5.
13. GUERNE PA, TERKELTAUB R, ZURAW B, LOTZ M: Inflammatory microcrystals stimulate interleukin-6 production and secretion by human monocytes and synoviocytes. *Arthritis Rheum* 1989; 32: 1443-52.
14. MARTINON F, PETRILLI V, MAYOR A, TARDIVEL A, TSCHOPP J: Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature* 2006; 440: 237-41.
15. FINCKH A, MC CARTHY GM, MADIGAN A *et al*.: Methotrexate in chronic-recurrent calcium pyrophosphate deposition disease: no significant effect in a randomized crossover trial. *Arthritis Res Ther* 2014; 16: 458.
16. KLEIBER BALDERRAMA C, ROSENTHAL AK, LANS D, SINGH JA, BARTELS CM: Calcium pyrophosphate deposition disease and associated medical comorbidities: a national cross-sectional study of US veterans. *Arthritis Care Res* (Hoboken) 2017; 69: 1400-6.
17. SCHILSKY RL, ANDERSON T: Hypomagnesemia and renal magnesium wasting in patients receiving cisplatin. *Ann Intern Med* 1979; 90: 929-31.
18. RICHETTE P, AYOUB G, LAHALLE S *et al*.: Hypomagnesemia associated with chondrocalcinosis: a cross-sectional study. *Arthritis Rheum* 2007; 57: 1496-501.
19. MACKAY JD, BLADON PT: Hypomagnesaemia due to proton-pump inhibitor therapy: a clinical case series. *QJM* 2010; 103: 387-95.
20. MURSHED M, SCHINKE T, MCKEE MD, KARSENTY G: Extracellular matrix mineralization is regulated locally; different roles of two gla-containing proteins. *J Cell Biol* 2004; 165: 625-30.
21. ABHISHEK A, DOHERTY S, MACIEWICZ R, MUIR K, ZHANG W, DOHERTY M: Association between low cortical bone mineral density, soft-tissue calcification, vascular calcification and chondrocalcinosis: a case-control study. *Ann Rheum Dis* 2014; 73: 1997-2002.
22. GERSTER JC, RAPPOPORT G, GINALSKI JM: Prevalence of periarticular calcifications in pyrophosphate arthropathy and their relation to nodal osteoarthrosis. *Ann Rheum Dis* 1984; 43: 255-7.