Clin Rheumatol (2001) 20:428–431

Clinical
Rheumatology

Original Article

Local Deposition of Calcium Pyrophosphate Crystals in Evolution of Knee Osteoarthritis

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Abstract: The aim of the study was to investigate the frequency of development of local calcium pyrophosphate (CPPD) crystal deposition in patients with knee OA initially found negative for these crystals, as well as to discover whether prognostic indicators for this subset of patients can be found. A clinical follow-up of records of outpatients with idiopathic knee OA was established. An anteroposterior plain radiography of the knee joints was made initially and at the end of the observation period. The follow-up period needed to be more than 1 year. Patients were divided into two groups. The first included patients with knee OA who did not develop intra-articular CPPD crystal deposition during the observation period (OA group). The second included those patients whose X-rays or synovial fluid (SF) analysis in the follow-up showed these crystal deposits to be present (OA + CPPD group). There were 59 patients (42 women, 17 men) who met the selection criteria. During the observation period (8.1 ± 7.4 years in the OA group, 10.4 ± 6 years in the OA + CPPD group), intra-articular CPPD deposits were observed in 15 patients (25%): 10 on the X-rays, eight in the SF and three in both examinations. Age at diagnosis of OA and incidence of obesity were similar in both groups. There was a trend ($P = 0.21$) towards men developing intra-articular CPPD crystal deposits more frequently than women. OA in only one knee joint was significantly more frequent in the group with CPPD ($P < 0.01$). Of those with CPPD deposits 40% required surgery at the end of the observation period, compared to 27.2% of those without deposits ($P = 0.27$). The waiting period before knee surgery was shorter in the OA + CPPD group but the difference was not statistically significant. In conclusion, local CPPD crystal deposition was observed in 25% of cases during the evolution of knee OA. No predictive factors were found. OA of the knee could, per se, favour the development of CPPD deposits. The occurrence of intra-articular CPPD deposits seemed to be related to a more rapid and severe evolution of OA of the knee.

Keywords: Articular chondrocalcinosis; CPPD crystal deposition disease; Knee osteoarthritis

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Introduction

Osteoarthritis (OA) and chondrocalcinosis are common rheumatic diseases, especially in elderly people. Predisposing factors such as a previously damaged joint [1,2], and metabolic diseases such as hypothyroidism [3] or haemochromatosis [4], have been described for both diseases. Although intra-articular calcium pyrophosphate dihydrate (CPPD) crystal deposition can be observed in advanced stages of OA [5–7], the occurrence of these crystal deposits during the evolution of OA has not yet been specifically evaluated.

The aim of this retrospective study was to investigate the frequency of the development of local CPPD crystal deposition in the knee joints of patients with knee OA initially found negative for these crystals, and to try to find out what factors could be considered as prognostic indicators for this subset of patients.

Patients and Methods

The records of all outpatients with idiopathic knee OA from the rheumatology departments in the above-mentioned hospitals were reviewed. The last consultation was some time between January 1995 and August 1999. The clinical and radiological follow- up period needed to be more than 1 year to include the patients in the study. All patients had to meet the ACR classification criteria for OA of the knee [8].

An anteroposterior plain radiograph of the knee joints was taken initially and at the end of the observation period. Femorotibial joint space narrowing [9], subchondral bone sclerosis and/or the presence of a marginal osteophyte (Fig. 1a) were the radiological criteria for diagnosis of OA of the knee joint. The presence of CPPD deposits on the X-rays was assumed when coarse granular calcifications of the menisci (Fig. 1b) or linear densities in the hyaline cartilage (chondrocalcinosis) were observed [10]. X-rays were read subsequently by two radiologists.

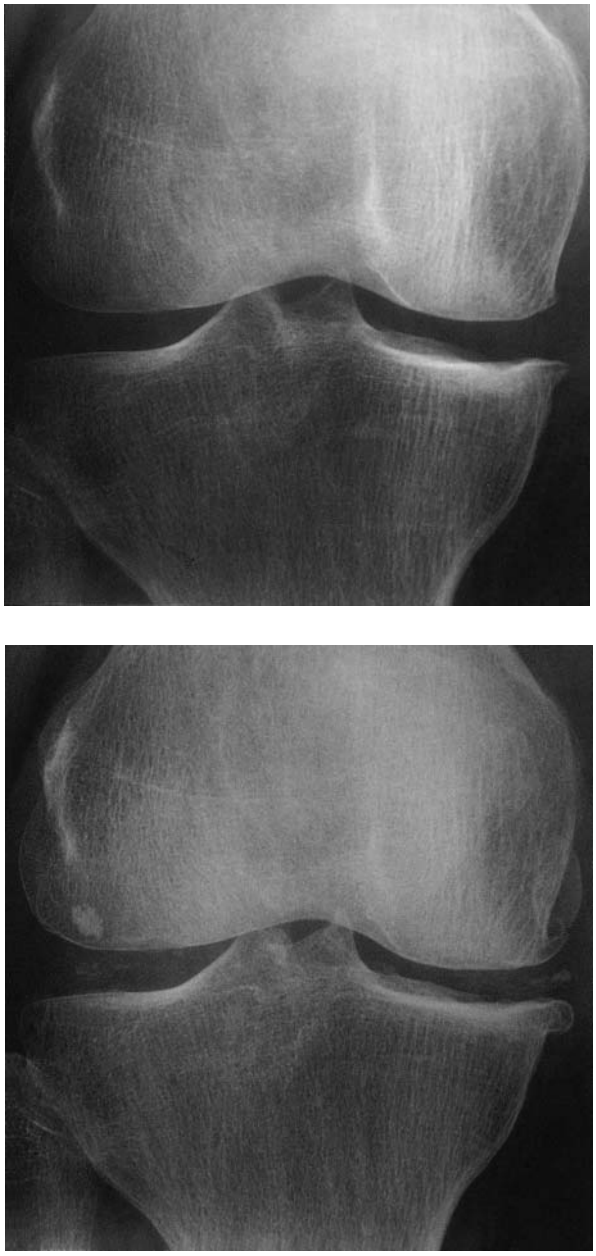

Fig. 1a Knee X-rays of a 65-year-old woman with medial femorotibial osteoarthritis. **b** Same knee 12 years later showing CPPD crystal deposits.

Synovial fluid (SF) analysis, including microscopic examination of a native drop of SF under polarised light, was performed in those cases who presented an effusion of the knee. CPPD crystals were considered present when crystals of rhomboid shape with weak positive birefringence were observed [10]. Patients with initial CPPD crystal deposits on the X-rays or in the SF and those with a history of previous meniscectomy were excluded.

Age at diagnosis of OA, body mass index (BMI), gender, uni- or bilateral involvement, and the presence of generalised OA as expressed by the number of other peripheral joints with OA [11] were the baseline characteristics of the selected patients that were taken into account. During the follow-up period, the moment when CPPD deposits were first discovered by X-ray or SF analysis was recorded. When surgery of the knee was believed to be necessary, the final clinical evaluation was made a short time before the operation. Patients were divided into two groups. The first included patients with OA of a knee who did not develop intra-articular CPPD deposits during the observation period (OA group). The second group included those patients whose follow-up X-rays or SF analysis showed these crystal deposits to be present (OA + CPPD group).

Statistics

Evaluation of patients was expressed as the mean ± the standard deviation (SD). Proportions between the two groups were compared using Pearson's χ^2 test, with Fisher's exact test when necessary. P values less than 0.05 were considered significant.

Results

Of the 227 patients with knee OA who consulted both our departments, 127 were excluded from the study because there was no follow-up and 41 were not included because they were found initially to present with CPPD crystal deposits. Only 59 patients (42 women, 17 men) who met the above-mentioned selection criteria were included in the study. During the follow-up period, intra-articular CPPD crystal deposits appeared in 15 patients (25%): 10 on the X-rays, eight in the SF and three in both examinations. Table 1 shows the baseline characteristics of both groups. The age at OA diagnosis and the body mass index (BMI) were similar in both groups. There was a trend ($P = 0.21$) towards men having a higher incidence

Table 1. Baseline characteristics of both groups of patients

	OA group (n = 44)	OA+CPPD group (n = 15)	P value
Age at OA diagnosis (years)	61.3±3.6	59.9±5.8	NS
BMI (kg/m^2)	29.4±1.4	29.6±3.2	NS
Gender (M/F)	11/33	9/6	0.21
Unilateral involvement of OA (%)	15	53	<0.01
Number of other peripheral joints with OA/patient	0.7±0.88	1.1±1.1	NS

Group OA, patients who did not develop local CPPD crystal deposition; Group OA + CPPD, patients whose X-rays or SF examination disclosed CPPD crystal deposits.

Table 2. Follow-up of both groups of patients

	OA group (n = 44)	OA+CPPD group (n = 15)	P value
Mean observation time (years)	8.1±7.4	10.4±6	NS
Knee surgery (%)	27.2	40	0.27
Interval between OA and knee surgery (years)	7.3±6.3	3±1.7	NS

of developing intra-articular CPPD crystal deposition than women. When comparing the patients who developed CPPD crystal deposition to those who did not, OA in only one knee joint was significantly more frequent in the group with CPPD ($P < 0.01$). The average number of other joints involved by OA was not significantly different between the two groups.

Table 2 shows the mean observation time and the surgical requirements for the two groups of patients. At the end of the observation period 40% of the patients with CPPD crystal deposition disease had to be operated on, versus 27.2% of those without CPPD deposition ($P = 0.27$). The time before surgery (arthroplasty in all cases) was shorter in the OA + CPPD group (3 ± 1.7 years) than in the OA without CPPD group (7.3 ± 6.3 years), but the difference was not statistically significant.

Illustrative Case

A 65-year-old woman reported mechanical pain in the right knee in 1985. There was no joint effusion but a slight impairment of the joint flexion. Figure 1a represents the initial X-ray of the right knee showing medial femorotibial OA. The follow-up was characterised by persistent knee pain despite treatment with NSAIDs, physiotherapy and local steroid injections. A new X-ray was performed in 1997 because of a flare-up of the pain without joint effusion (Fig. 1b); a moderate worsening of the OA and an image of diffuse CPPD deposition disease in the knee joint were observed.

Discussion

The number of patients included in our study was low but close to those reported in the other few studies concerning the natural course of knee OA; [12–15]. Therefore, our results have also to be taken with caution. Massardo et al. [12] indicated that the incidence of chondrocalcinosis in an 8-year prospective follow-up of 31 patients with knee OA was 6.5%. In a previous study, Hernborg et al. [13] found that in a cohort of 84 patients 13.2% of knee joints with OA developed chondrocalcinosis after a mean of 13 years. In our series of patients with knee OA initially found negative for crystals, after an 8-year follow-up period 10 patients (17%) showed radiological deposits of CPPD crystals. Moreover, the analysis of the SF disclosed five additional cases (8%), none of them having shown CPPD deposits on the X-rays. Compared to the literature [12,13,16], our retrospective study showed a higher proportion (25%) of patients with knee OA initially negative for CPPD crystals who developed evidence of local deposition of these crystals during the observation period. However, our results are closer to those of Hernborg et al. [13], although the duration of follow-up was shorter in our series.

There are some hypotheses to explain this relative high proportion of cases: CPPD crystal deposits could have been present but not apparent on the initial X-rays [7,17] and a joint effusion for SF analysis was not always present when the diagnosis of knee OA was made. There could also have been a selection bias related to the retrospective nature of our study. Another possible bias could be that patients with a poor evolution preferentially sought advice from rheumatologists during the follow-up period. Also, we can not exclude the possibility that a diffuse CPPD deposition disease was initially present, affecting joints other than the knees; an extensive radiological survey was not made at the first visit. Nor in the other clinical studies published on the same subject was an extensive joint radiological examination performed.

The relationship between OA and CPPD crystal deposition disease can be questioned, as OA could by itself favour the local development of CPPD deposits [18]: in the cartilage, the formation of CPPD crystals

could occur when increased amounts of soluble pyrophosphate (PPi) are in the presence of nucleating and growth-promoting factors [3,19,20]. Likewise, the down-regulation of inhibitory factors of nucleation, such as proteoglycans in the matrix of joints with OA [21], could promote the deposition of these crystals. The release of higher quantities of PPi when the chondrocytes are hypertrophied in the early stages of OA could also favour the deposition of CPPD crystals. So also could a reduced activity of some ectoenzymes on the chondrocyte membrane metabolising PPi in the later stages of OA. The high frequency of patients with unilateral knee involvement in the OA + CPPD group of our study seems also to corroborate the predisposing role of OA in local CPPD deposition.

The high frequency (25%) of CPPD crystal deposition in our series of patients with knee OA supports the idea that there is some causal relationship between both conditions; indeed, the prevalence of CPPD crystal deposition of the knee in the general population of the same age without OA is much lower (10%–15%) [1,6,7,22,23]. The question whether obesity could play a role in CPPD crystal deposition was addressed. The mean BMI was slightly increased in both groups of patients, but we found no significant difference between the OA + CPPD group and the OA group (Table 1). So, in our series obesity is unlikely to have played any role in the development of CPPD deposits. We noticed that there was a trend towards men having a higher incidence of CPPD crystal deposition; this is in agreement with some data in the literature, a male predominance having sometimes been reported in large series of patients [24].

Local deposition of CPPD crystals in OA knee joints is associated with a poorer prognosis [3,12]. We noticed that a higher proportion of patients in the OA + CPPD group required surgery at the end of the observation time (Table 2), suggesting that detecting CPPD crystal deposits on radiographs or in SF specimens of patients with knee OA could be clinically relevant. The evolution of cases with CPPD crystal deposition is often not favourable. As already reported in other studies, a poor outcome of the evolution of cases with CPPD crystal deposition can be predicted.

References

1. Felson DT. The epidemiology of knee osteoarthritis: results from the Framingham Osteoarthritis Study. Semin Arthritis Rheum 1990;20(suppl 1):42–50.
2. Settas L, Doherty M, Dieppe P. Localised chondrocalcinosis in unstable joints. Br Med J 1982;285:175–6.
3. Doherty M. Pyrophosphate arthropathy. Recent clinical advances. Ann Rheum Dis 1983;42(suppl 1):38–44.
4. Caswell A, Guilland-Cumming DF, Hearn PR, Mc Guire MK, Russell RG. Pathogenesis of chondrocalcinosis and pseudogout. Metabolism of inorganic pyrophosphate and production of calcium pyrophosphate dihydrate crystals. Ann Rheum Dis 1983;42(suppl):27–37.
5. Dieppe P, Watt I. Crystal deposition in osteoarthritis: an opportunistic event? Clin Rheum Dis 1985;11:367–92.
6. Sanmarti R, Panella D, Brancos MA et al. Prevalence of articular chondrocalcinosis in elderly subjects in a rural area of Catalonia. Ann Rheum Dis 1993;52:418–22.
7. Wilkins E, Dieppe P, Maddison P, Evison G. Osteoarthritis and articular chondrocalcinosis in the elderly. Ann Rheum Dis 1983;42:280–4.
8. Altman R, Asch E, Bloch G et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039–49.
9. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. Ann Rheum Dis 1957;16:494–501.
10. McCarty DJ. Calcium pyrophosphate dihydrate crystal deposition disease. Arthritis Rheum 1976;19:275–85.
11. Kellgren JH, Moore R. Generalised osteoarthritis and Heberden's nodes. Br Med J 1952;1:181–7.
12. Massardo L, Watt I, Cushnaghan J, Dieppe P. Osteoarthritis of the knee joint: an eight-year prospective study. Ann Rheum Dis 1989;48:893–7.
13. Hernborg J, Linden B, Nilsson BE. Chondrocalcinosis: a secondary finding in osteoarthritis of the knee. Geriatrics 1977;32:123–6.
14. Spector TD, Dacre JE, Harris PA, Huskisson EC. Radiological progression of osteoarthritis: an 11 year follow-up study of the knee. Ann Rheum Dis 1992;51:1107–10.
15. Sahlström A, Johnell O, Redlund-Johnell I. The natural course of arthrosis of the knee. Clin Orthop Rel Res 1997;340:152–7.
16. Dougados M, Gueguen A, Nguyen M et al. Longitudinal radiologic evaluation of osteoarthritis of the knee. J Rheumatol 1992;19:378–84.
17. Bardin T, Fritz P, Lioté P. Arthrites microcristallines. EULAR Bull 1994;23:49–54.
18. Stankovic A, Mitrovic D, Morin J et al. Relations entre la chondrocalcinose articulaire et l'arthrose du genou chez le sujet âgé. Rhumatologie 1982;34:35–9.
19. Wright GD, Doherty M. Calcium pyrophosphate crystal deposition is not always 'wear and tear' or aging. Ann Rheum Dis 1997;56:586–8.
20. Bardin T. Advances in mechanisms of crystal-induced inflammation. EULAR Bull 1985;14:13–15.
21. Brandt KD. La pathogénie de l'arthrose. EULAR Bull 1992;21:80–7.
22. Ellman MH, Brown NL, Levin B. Prevalence of knee chondrocalcinosis in hospital and clinic patients aged 50 or older. J Am Geriatr Soc 1981;29:189–92.
23. Mitrovic D, Stankovic A, Morin J et al. Fréquence anatomique de la ménisco-chondrocalcinose du genou. Rev Rhum 1982;49:495–9.
24. McCarty DJ. Calcium pyrophosphate crystal deposition disease. Arthritis and allied conditions. Philadelphia: Lea & Febiger, 1979:1282.

Received for publication 25 October 2000
Accepted in revised form 18 June 2001