

# European League Against Rheumatism recommendations for calcium pyrophosphate deposition. Part I: terminology and diagnosis

W Zhang,<sup>1</sup> M Doherty,<sup>1</sup> T Bardin,<sup>2</sup> V Barskova,<sup>3</sup> P-A Guerne,<sup>4</sup> T L Jansen,<sup>5</sup> B F Leeb,<sup>6</sup> F Perez-Ruiz,<sup>7</sup> J Pimentao,<sup>8</sup> L Punzi,<sup>9</sup> P Richette,<sup>2</sup> F Sivera,<sup>10</sup> T Uhlig,<sup>11</sup> I Watt,<sup>12</sup> E Pascual<sup>13</sup>

<sup>1</sup>Academic Rheumatology, University of Nottingham, Nottingham, UK

<sup>2</sup>University Paris 7, Fédération de Rhumatologie, Hôpital Lariboisière, Paris, France

<sup>3</sup>Crystal Arthritis Department, State Institute of Rheumatology, Moscow, Russia

<sup>4</sup>Division of Rheumatology, University Hospital of Geneva, Geneva, Switzerland

<sup>5</sup>Department of Rheumatology, University Medical Centre Nijmegen St Radboud, Nijmegen, The Netherlands

<sup>6</sup>Second Department of Medicine, Centre for Rheumatology Lower Austria, Stockerau, Austria

<sup>7</sup>Sección de Rheumatología, Hospital de Cruces, Baracaldo, Spain

<sup>8</sup>Department of Rheumatology, Egas Moniz Hospital, Lisbon, Portugal

<sup>9</sup>Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Padova, Italy

<sup>10</sup>Department of Rheumatology, Hospital General de Alicante, Alicante, Spain

<sup>11</sup>Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

<sup>12</sup>Department of Radiology, Leiden University Medical Centre, Leiden, The Netherlands

<sup>13</sup>Sección de Rheumatología, Hospital General Universitario de Alicante, Alicante, Spain

## Correspondence to

Dr Weiya Zhang, Academic Rheumatology, University of Nottingham, Clinical Sciences Building, City Hospital, Nottingham NG5 1PB, UK; [weiya.zhang@nottingham.ac.uk](mailto:weiya.zhang@nottingham.ac.uk)

Accepted 11 November 2010  
Published Online First  
7 January 2011

## ABSTRACT

**Objectives** To agree terminology and to develop recommendations for the diagnosis of calcium pyrophosphate deposition (CPPD).

**Methods** The European League Against Rheumatism (EULAR) CPPD Task Force, comprising 15 experts from 10 countries, agreed the terms and recommendations for diagnosis of CPPD using a Delphi consensus approach. Evidence was systematically reviewed and presented in terms of sensitivity, specificity and positive likelihood ratio (LR) to support diagnosis; ORs were used for association. Strength of recommendation (SOR) was assessed by the EULAR visual analogue scale.

**Results** It was agreed that 'CPPD' should be the umbrella term that includes acute calcium pyrophosphate (CPP) crystal arthritis, osteoarthritis (OA) with CPPD and chronic CPP crystal inflammatory arthritis.

Chondrocalcinosis (CC) defines cartilage calcification, most commonly due to CPPD and detected by imaging or histological examination. A total of 11 key recommendations were generated on the topics of clinical features, synovial fluid (SF) examination, imaging, comorbidities and risk factors. Definitive diagnosis of CPPD relies on identification of SF CPP crystals. Rapid onset inflammatory symptoms and signs are suggestive but not definitive for acute CPP crystal arthritis.

Radiographic CC is not highly sensitive or specific, whereas ultrasonography appears more useful (LR=24.2, 95% CI 3.51 to 168.01) for peripheral joints. Recognised risk factors for CPPD include ageing, OA and metabolic conditions such as primary hyperparathyroidism, haemochromatosis and hypomagnesaemia; familial forms are rare. SORs varied from 53 to 99 (maximum 100).

**Conclusion** New terms for CPPD were agreed and 11 key recommendations for diagnosis of CPPD were developed using research evidence and expert consensus.

## INTRODUCTION

Calcium pyrophosphate deposition (CPPD) occurs almost exclusively in articular tissues, most commonly fibrocartilage and hyaline cartilage,<sup>1</sup> and is the most common cause of chondrocalcinosis (CC). Calcium pyrophosphate (CPP) associated arthritis is the third most common inflammatory arthritis.<sup>2</sup> Recognised risk factors are ageing, osteoarthritis (OA), previous joint trauma/injury, metabolic disease and familial predisposition.<sup>3,4</sup>

The complexity of CPPD in terms of variable phenotypes is compounded by use of different

terminologies and classification. In 1961 McCarty and colleagues first identified CPP crystals in synovial fluid (SF) from knees of patients with acute synovitis and CC,<sup>5</sup> introducing the term 'CPPD' for 'calcium pyrophosphate dihydrate' crystals.<sup>6</sup> Similarity to gout prompted the term 'pseudogout' for this 'crystal-induced arthropathy'. Subsequently other presentations were recognised, many appearing to mimic other forms of arthritis, encouraging proliferation of 'pseudo' syndromes and a complex clinical classification of 'pseudogout' (type A), 'pseudo-rheumatoid arthritis' (type B), 'pseudo-osteoarthritis' (with acute attacks, type C; without inflammation, type D), 'lanthanic or asymptomatic' (type E) and 'pseudoneuropathic' (type F), to which other forms were later added.<sup>7</sup> The term 'CPPD crystal deposition disease' was introduced to incorporate all instances of CPP deposition, even though CPPD does not always appear injurious or causal in 'disease'. The term 'pyrophosphate arthropathy' (PA) was later used, particularly in Europe, for CPPD with accompanying structural arthritis.<sup>4</sup> However, some clinicians use the terms CC or pseudogout for any phenotype, whereas others restrict CC for radiographic calcification, pseudogout for acute synovitis and PA for CPPD plus OA.<sup>3,8</sup>

The group that developed European League Against Rheumatism (EULAR) recommendations for gout<sup>9,10</sup> considered it desirable to agree a uniform terminology for CPPD and to address issues relating to diagnosis and management. Therefore, the EULAR CPPD Task Force was formed to produce evidence-based recommendations using a combined systematic review and expert consensus approach.<sup>11</sup> Part I, terminology and diagnosis, is presented here.

## METHODS

### Expert consensus

The Task Force comprised 15 experts from 10 countries. A meeting was organised to agree terminology; subsequently, preagreed terms were circulated for voting. Each participant independently submitted up to 10 propositions on key aspects of diagnosis; consensus was reached using the Delphi technique.<sup>9,12</sup> A second meeting was organised to discuss recommendations and supporting evidence and to score strength of recommendations (SORs).<sup>13,14</sup>

## Recommendations

### Systematic review of research evidence

As with previous projects,<sup>9</sup> research evidence for each proposition was systematically searched (January 1950 to January 2009). Search terms included: calcium pyrophosphate dihydrate and/or deposition, CC, PA, pseudogout, crystal associated diseases/arthropathy/arthritis, crystal deposition diseases and calcium crystals. Studies informing diagnosis of CPPD were included. Case reports, reviews, editorials and commentaries were excluded.

Wherever possible, sensitivity, specificity, likelihood ratios (LR), probability of CPPD and reliability ( $\kappa$  or intraclass correlation coefficient) were calculated for diagnostic tests; RRs or ORs were estimated for association.<sup>9</sup> Statistical pooling was undertaken as appropriate and a random effects model was used for heterogenous results.<sup>15</sup> The EULAR level of evidence (LOE) for diagnosis,<sup>9</sup> and EULAR 0–100 mm visual analogue scale (VAS)<sup>13 14</sup> were used to rank LOE and SOR.

### Future research agenda

After the second meeting each participant submitted independently up to 10 future research propositions; consensus was obtained by the Delphi technique.

## RESULTS

### Terminology of CPPD and its related conditions

The following terms and definitions were agreed:

1. CPP crystals: the simplified term for calcium pyrophosphate dihydrate crystals (similar to 'sodium urate' for monosodium urate monohydrate crystals)
2. CPPD: the umbrella term for all instances of CPP crystal occurrence.

3. CC: cartilage calcification, identified by imaging or histological examination. This is not always due to CPPD and may occur as an isolated finding in an apparently otherwise normal joint or coexist with structural changes resembling OA.
4. Clinical presentations associated with CPPD:
  - ▶ Asymptomatic CPPD: CPPD with no apparent clinical consequence. This may be isolated CC, or OA with CC. Often this is identified incidentally following imaging for other reasons.
  - ▶ OA with CPPD: CPPD in a joint that also shows changes of OA, on imaging or histological examination.
  - ▶ Acute CPP crystal arthritis: acute onset, self-limiting synovitis with CPPD (replacing the term 'pseudogout').
  - ▶ Chronic CPP crystal inflammatory arthritis: chronic inflammatory arthritis associated with CPPD.
5. Risk factors that, if present, may be noted in phenotype characterisation:
  - ▶ Previous joint injury.
  - ▶ Hereditary/familial predisposition to CPPD.
  - ▶ Specific diseases (eg, haemochromatosis, primary hyperparathyroidism, hypophosphatasia, hypomagnesaemia).

### EULAR recommendations

Of 102 initial propositions, 11 were agreed after 2 Delphi rounds. Recommendations covered four domains: clinical features, SF, imaging and risk factors/associations (see table 1 for the full

**Table 1** Propositions and strength of recommendation (SOR), ordered according to topic (clinical features, synovial fluid, imaging, comorbidities and risk factors)

No.	Proposition	LoE	SOR (95% CI)
1	Although often asymptomatic, CPPD can present variable clinical phenotypes, most commonly OA with CPPD, acute CPP crystal arthritis and chronic inflammatory arthritis.	IIb	90 (86 to 94)
2	The rapid development of severe joint pain, swelling and tenderness that reaches its maximum within 6–24 h, especially with overlying erythema, is highly suggestive of acute crystal inflammation though not specific for acute CPP crystal arthritis.	IV	88 (84 to 93)
3	Presentation with features suggesting crystal inflammation involving the knee, wrist or shoulder of a patient over age 65 years is likely to be acute CPP crystal arthritis. The presence of radiographic CC and advanced age increases this likelihood, but definitive diagnosis needs to be crystal proven.	IIb	81 (74 to 89)
4	OA with CPPD particularly targets knees with chronic symptoms and/or acute attacks of crystal-induced inflammation. Compared to OA without CPPD, it may associate with more inflammatory symptoms and signs, an atypical distribution (eg, radiocarpal or midcarpal, glenohumeral, hindfoot or midfoot involvement) and prominent cyst and osteophyte formation on radiographs.	Ib/IIb	53 (38 to 68)
5	Chronic CPP crystal inflammatory arthritis presents as chronic oligoarthritis or polyarthritis with inflammatory symptoms and signs and occasional systemic upset (with elevation of CRP and ESR); superimposed flares with characteristics of crystal inflammation support this diagnosis. It should be considered in the differential diagnosis of rheumatoid arthritis and other chronic inflammatory joint diseases in older adults. Radiographs may assist diagnosis, but the diagnosis should be crystal proven.	IIb	83 (72 to 93)
6	Definitive diagnosis of CPPD is by identification of characteristic CPP crystals (parallelepipedic, predominantly intracellular crystals with absent or weak positive birefringence) in synovial fluid, or occasionally biopsied tissue.	Ib	94 (90 to 97)
7	A routine search for CPP (and urate) crystals is recommended in all synovial fluid samples obtained from undiagnosed inflamed joints, especially from knees or wrists of older patients.	IV	99 (97 to 100)
8	Radiographic CC supports the diagnosis of CPPD, but its absence does not exclude it.	IIb	97 (92 to 102)
9	Ultrasonography can demonstrate CPPD in peripheral joints, appearing typically as thin hyperechoic bands within hyaline cartilage and hyperechoic sparkling spots in fibrocartilage. Sensitivity and specificity appear excellent and possibly better than those of conventional x-rays.	IIb	78 (70 to 87)
10	Acute CPP crystal arthritis and sepsis may coexist, so when infection is suspected microbiological investigation should be performed even if CPP crystals and/or CC are identified.	III	96 (93 to 100)
11	In patients with CPPD, risk factors and associated comorbidities should be assessed, including OA, prior joint injury, predisposing metabolic disease (including haemochromatosis, primary hyperparathyroidism, hypomagnesaemia) and rare familial predisposition. Metabolic or familial predisposition should particularly be considered in younger patients (<55) and if there is florid polyarticular CC.	Ib/IIb	94 (89 to 99)

CC, chondrocalcinosis; CPP, calcium pyrophosphate; CPPD, calcium pyrophosphate deposition; ESR, erythrocyte sedimentation rate; LoE, level of evidence (Ia=meta-analysis of cohort studies, Ib=meta-analysis of case control or cross sectional studies, IIa=cohort study, IIb=case control or cross-sectional studies, III=non-comparative descriptive studies, IV=expert opinion); OA, osteoarthritis; SOR, strength of recommendation on visual analogue scale (0–100 mm, 0=not recommended at all, 100=fully recommended).

**Table 2** Validity of diagnostic tests for calcium pyrophosphate deposition (CPPD)

Test	Target joints	No. studies (subjects)	Age range, years	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR(95% CI)	References
Clinical								
Acute CPP crystal arthritis								
Acute attacks	Knee	1 (100)	36–80	Radiographic CC	0.50 (0.28 to 0.72)	0.90 (0.83 to 0.97)	5.00 (2.27 to 11.02)	Doherty et al <sup>32</sup>
Chronic CPP crystal inflammatory arthritis								
Pain	Knee, wrist, elbow, shoulder and hip	4 (429)	36–97	SF crystals and/or radiographic CC	0.21 (0.12 to 0.30)	0.80 (0.72 to 0.89)	1.18 (0.82 to 1.71)	Gordon et al <sup>1</sup> Doherty et al <sup>32</sup> Wilkins et al <sup>36</sup> Viriyavejkul et al <sup>77</sup>
Stiffness	Knee	2 (227)	36–80	Radiographic CC	0.35 (0.19 to 0.50)	0.81 (0.74 to 0.88)	1.96 (1.12 to 3.44)	Gordon et al <sup>1</sup> Doherty et al <sup>32</sup>
Swelling/effusion	Knee, wrist, elbow, shoulder and hand	5 (432)	36–97	Radiographic CC	0.40 (0.23 to 0.56)	0.77 (0.68 to 0.87)	1.56 (1.16 to 2.11)	Gordon et al <sup>1</sup> Doherty et al <sup>32</sup> Wilkins et al <sup>36</sup> Utsinger et al <sup>44</sup> Hansen and Herning <sup>55</sup>
Tenderness	Knee	2 (227)	36–80	Radiographic CC	0.13 (0.02 to 0.24)	0.85 (0.79 to 0.91)	0.91 (0.37 to 2.24)	Gordon et al <sup>1</sup> Doherty et al <sup>32</sup>
Instability	Knee	2 (227)	36–80	Radiographic CC	0.18 (0.06 to 0.31)	0.82 (0.51 to 1.14)	0.95 (0.44 to 2.04)	Gordon et al <sup>1</sup> Doherty et al <sup>32</sup>
Synovial fluid								
CPP crystals	Not specified	194		Expert diagnosis	0.95 (0.92 to 1.00)	0.86 (0.80 to 0.93)	7.09 (4.27 to 11.76)	Lumbreras et al <sup>59</sup>
Radiograph CC	Wrist	18	71 (41–95)	CPP crystals	0.29 (–0.05 to 0.62)	0.20 (–0.15 to 0.55)	0.36 (0.10 to 1.25)	Utsinger et al <sup>44</sup>
Ultrasound								
Cartilage calcification	Knee	43	68 (40–92)	CPP crystals	0.87 (0.69 to 1.04)	0.96 (0.90 to 1.03)	24.2 (3.51 to 168.01)	Filippou et al <sup>62</sup>
Achilles tendon calcification	Heel	107	65 (42–92)	Radiographic CC plus CPP crystals	0.56 (0.45 to 0.71)	0.98 (0.94 to 1.02)	29 (4.11 to 204.05)	Falsetti et al <sup>78</sup>
Plantar fascia calcification	Heel	107	65 (42–92)	Radiographic CC plus CPP crystals	0.16 (0.06 to 0.25)	0.98 (0.94 to 1.02)	7.89 (1.04 to 60.16)	Falsetti et al <sup>78</sup>

CC, chondrocalcinosis; CPP, calcium pyrophosphate; LR, likelihood ratio.

propositions). Evidence regarding validity for each test/feature are summarised in table 2, and risk factors and associations in table 3.

### Clinical features

#### Proposition 1 (also see detailed proposition in table 1)

CC may be an apparently isolated phenomenon or occur with structural changes of OA.<sup>16–18</sup> Hospital-based series suggest that OA with CPPD may differ from OA without CPPD in showing more osteophytosis,<sup>18–21</sup> different joint involvement<sup>22–26</sup> and more inflammatory features (table 3). However, whether OA with CPPD is a distinct OA ‘subset’ remains unclear. Isolated CC and OA with CPPD may be clinically occult or associate with acute CPP crystal arthritis; OA with CPPD may also associate with pain, stiffness and functional limitation. Much less commonly, atypical or periarticular CPPD may associate with tendinitis,<sup>27</sup> tenosynovitis,<sup>28</sup> bursitis,<sup>29</sup> tumorous CPPD<sup>30</sup> or syndromes relating to spinal involvement<sup>31</sup>

#### Proposition 2

Direct literature evidence to support this recommendation was not found. However, one nested case-control study of postmeniscectomy knees showed those with CC had five times more risk (LR=5.00, 95% CI 2.27 to 11.02) of self-limiting acute attacks compared to those without CC.<sup>32</sup> One hospital series observed that in acute CPP crystal arthritis symptoms and signs usually resolve within 3–4 days.<sup>33</sup> Rapid development of acute synovitis with pain, stiffness, swelling/effusion and marked tenderness ( $\pm$ erythema) is highly characteristic of crystal synovitis but these

features are not specific to one crystal<sup>9</sup> so crystal identification is required for precise diagnosis.

#### Proposition 3

A community cross-sectional survey in Sweden found that CC is most common in knees (8.5%), then wrists (5.1%) and hands (1.7%).<sup>34</sup> Prevalence of knee CC in this study was similar to that in the USA (8.1%)<sup>17</sup> and UK (7.0%)<sup>18</sup> studies so this distribution may be generalisable to other populations. Several hospital series report similar distribution but greater prevalence for each joint<sup>1 35 36</sup> (figure 1). The glenohumeral joint appears less commonly affected.<sup>35</sup>

Ageing is a major risk factor. CPPD is rare under age 50,<sup>18</sup> but increases dramatically afterwards<sup>2 17 18 36–40</sup> (figure 2). The risk doubles every decade between 45 and 85 years (OR=2.25, 95% CI 1.79 to 2.82) independently of other risk factors.<sup>41</sup> CPPD under age 45 should raise the possibility of familial<sup>42 18 43</sup> or metabolic disease predisposition, especially if polyarticular. Gout is the main differential diagnosis of acute CPP crystal arthritis. Gout prevalence also increases with age,<sup>9</sup> but the first attack classically involves joints in the feet, (especially first metatarsophalangeal).<sup>9</sup> However, the first attack can affect the knee, and rarely the wrist, but the relative likelihood of urate or CPP crystal-induced synovitis according to site and age has not been calculated. Radiographic CC is often taken as a surrogate for CPPD but does not necessarily predict SF CPP crystal identification according to limited evidence for the wrist<sup>44</sup> (table 2) and the knee.<sup>35 45</sup> Definitive diagnosis of CPPD has to

## Recommendations

**Table 3** Risk factors and comorbidities associated with calcium pyrophosphate deposition (CPPD)

	No. studies	No. subjects	OR (95% CI)*	References
Age (every 10 years from 40 to 90)	1	1851	2.25 (1.79 to 2.82)	Zhang et al <sup>41</sup>
Female gender	8	5042	0.89 (0.58 to 1.38)	Gordon et al <sup>1</sup> Felson et al <sup>17</sup> Neame et al <sup>18</sup> Cruz et al <sup>34</sup> Doherty et al <sup>38</sup> Viriyavejikul et al <sup>77</sup> Ellman et al <sup>79</sup> Sanmartí et al <sup>80</sup>
BMI (WHO grade)	1	1851	0.90 (0.70 to 1.14)	Zhang et al <sup>41</sup>
Familial aggregation	2	2000	1.10 (0.58 to 2.08)	Zhang et al <sup>41</sup> Fernandez Dapica and Gómez-Reino <sup>76</sup>
OA	9	4517	2.66 (2.00 to 3.54)	Gordon et al <sup>1</sup> Felson et al <sup>17</sup> Neame et al <sup>18</sup> Riestra et al <sup>20</sup> Doherty et al <sup>38</sup> Al-Arfa <sup>49</sup> Menkes et al <sup>50</sup> Sanmartí et al <sup>51</sup> Stucki et al <sup>52</sup>
OST	3	1906	1.26 (0.76 to 2.09)	Neame et al <sup>18</sup> Bourqui et al <sup>54</sup> Hansen et al <sup>55</sup>
JSN	4	2043	1.24 (0.91 to 1.69)	Neame et al <sup>18</sup> Riestra et al <sup>20</sup> Schouten et al <sup>21</sup> Bourqui et al <sup>54</sup>
Cysts	3	367	2.94 (0.92 to 4.96)	Ledingham et al <sup>53</sup> Bourqui et al <sup>54</sup> Hansen et al <sup>55</sup>
Trauma/injury	1	100	5.00 (1.77 to 14.11)	Doherty et al <sup>32</sup>
RA	2	818	0.18 (0.08 to 0.41)	Doherty et al <sup>38</sup> Brasseur et al <sup>56</sup>
Hyperparathyroidism	5	976	3.03 (1.15 to 8.02)	Yashiro et al <sup>40</sup> Alexander et al <sup>66</sup> Huaux et al <sup>67</sup> Pritchard and Jessop <sup>68</sup> Rynes and Merzig <sup>69</sup>
Hypomagnesaemia	1	144	13.5 (2.76 to 127.3)	Richette et al <sup>72</sup>
Diuretics	1	1727	2.17 (1.02 to 4.19)	Neame et al <sup>18</sup>

\*Meta-analysis was undertaken to pool results from multiple studies

BMI, body mass index; JSN, joint space narrowing; OA, osteoarthritis; OST, osteophyte; RA, rheumatoid arthritis.

be crystal proven usually by examination of SF (occasionally histological).

#### Proposition 4

The knee is a target site for OA<sup>46–48</sup> and the most common site for CPPD<sup>1 34–36</sup> (figure 1). A total of 4 cross-sectional and 5 case-control studies (4517 subjects in all) provided quantitative data for analysis of the association between OA and CPPD.<sup>1 17 18 20 38 49–52</sup> The pooled OR was 2.66 (95% CI 2.00 to 3.54). Results were consistent between cross-sectional (2.52, 95% CI 1.86 to 3.44) and case-control (2.80, 95% CI 1.44 to 5.47) studies, suggesting people with OA are three times more likely to have CPPD.

CPPD may associate with more inflammatory features (eg, pain, stiffness, effusion, more severe pain and disability) and more rapid progression<sup>53</sup> than in knees without CPPD, but the associations are marginal and not useful for diagnosis (table 2).

CPPD may associate with an atypical distribution of OA. Compared with isolated OA, OA with CPPD may occur in less typical locations (eg, radiocarpal joints, elbows) and show more patellofemoral compartment involvement.<sup>22 26 25</sup> Triangular fibrocartilage CC and calcification of intrinsic carpal ligaments (particularly lunotriquetral) and capsules is also seen;<sup>24</sup> calcification of the gastrocnemius tendon origin may also associate with CPPD in knees.<sup>25</sup> Other sites of CC include the pubic symphysis and

hip labrum.<sup>23</sup> It is unknown whether CPPD within an individual associates with atypical OA (systemic association), or whether atypical OA only occurs in joints with CPPD (local association).

Whether osteophytosis is a characteristic of CPPD is unclear. One community study found the main association between OA and CC was with osteophyte, not joint space narrowing (JSN).<sup>18</sup> This is supported by some<sup>19–21</sup> but not other studies.<sup>54 55</sup> Overall pooled ORs were 1.26 (95% CI 0.76 to 2.09) for osteophyte and 1.24 (95% CI 0.91 to 1.69) for JSN (table 3). However, studies for osteophyte were heterogeneous ( $p=0.0004$ ) whereas those for JSN were homogenous ( $p=0.10$ ). Similarly the association with cysts remains uncertain (OR=2.94, 95% CI 0.92 to 4.96) (table 3).

#### Proposition 5

Although the population prevalence is unknown, hospital series of chronic CPP crystal inflammatory arthritis show that most are mono/oligoarthritis (89%) though some (11%) are polyarticular.<sup>55</sup> There may be non-specific elevation of C reactive protein and erythrocyte sedimentation rate<sup>53</sup> but diagnostically, identification of CC is more useful since this mainly results from CPPD and is less likely to occur with rheumatoid arthritis (OR=0.18, 95% CI 0.08 to 0.41)<sup>38 56</sup> (table 3). Nevertheless, definitive diagnosis relies on CPP crystal identification, usually in SF.

**SF examination****Proposition 6**

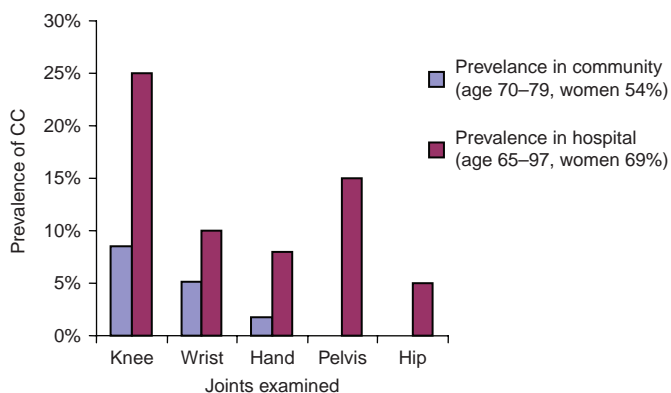
Identification of SF CPP crystals (usually by light, compensated polarised light or phase contrast microscopy) is the recommended reference standard for diagnosis of CPP crystal-associated arthritis (figure 3). First suggested by McCarty in 1962,<sup>57</sup> this has been used repeatedly as a major diagnostic feature for CPP syndromes.<sup>4</sup> Its validity and reliability have been systematically reviewed.<sup>58</sup> Training in SF CPP crystal identification results in better sensitivity (0.95, 95% CI 0.92 to 1.02) and reasonable specificity (0.86, 95% CI 0.80 to 0.93) compared to expert ('gold standard') identification<sup>59</sup> (table 2). Trained observer reliability is very good ( $\kappa=0.79$ , 95% CI not reported).<sup>59</sup> No quantitative cut-off of crystals is recommended; even one or a few crystals are clinically significant. The more characteristic the crystal morphology, the more confident the diagnosis.

**Proposition 7**

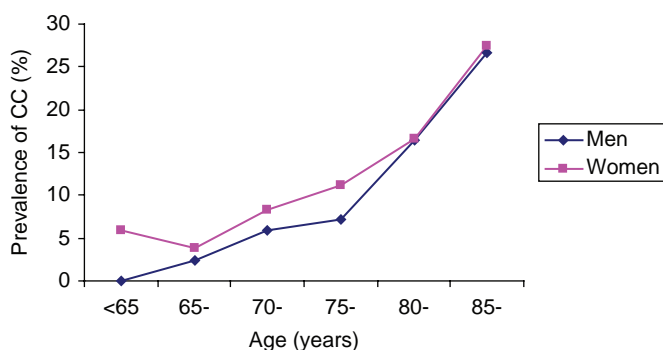
Although there are no specific studies, examination of SF for CPP crystals should be undertaken for any undiagnosed inflammatory arthritis since CPPD is a common cause of joint inflammation<sup>2</sup> and may present atypically.

**Imaging****Proposition 8**

Radiographic CC is a useful imaging marker, often taken as a surrogate for CPPD (figure 4), but common discordance with positive SF crystal identification reduces its diagnostic usefulness.<sup>35 44 45 60</sup> Detection of CC in proven cases of CPP crystal arthritis varies from 29% to 93% depending on population and

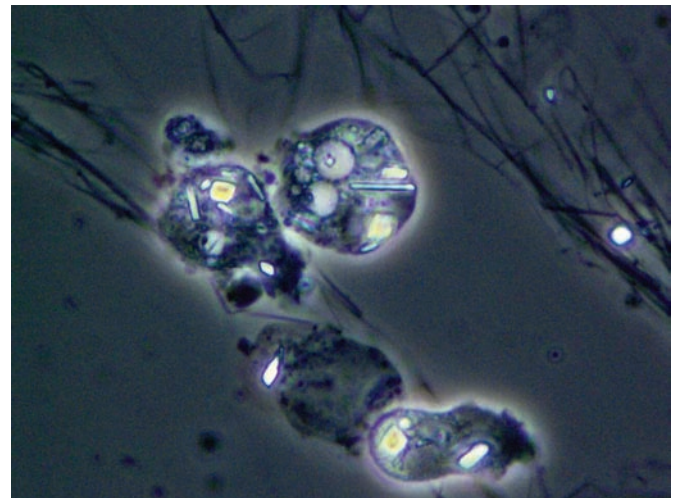


**Figure 1** Prevalence of chondrocalcinosis in different joints (data were calculated from Bergstrom *et al* 1986 and Wilkins *et al* 1983 studies<sup>34 36</sup>).

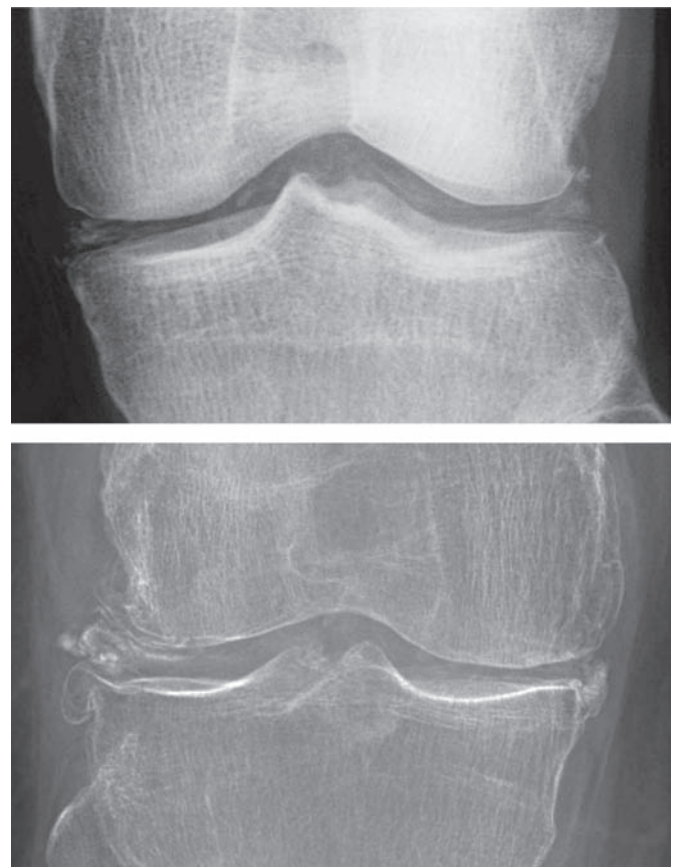


**Figure 2** Prevalence of knee chondrocalcinosis by age and gender (data obtained from Felson *et al* 1989<sup>17</sup>).

joint examined.<sup>35 44 45 60</sup> The sensitivity and specificity of CC against the 'gold' standard remain unknown. However, one small case control study (n=18)<sup>44</sup> suggested that at the wrist CC is neither sensitive (0.29) nor specific (0.20) for diagnosis (table 2); the likelihood of a patient with wrist CC having SF CPP crystals identified was only 3%. However, results of this

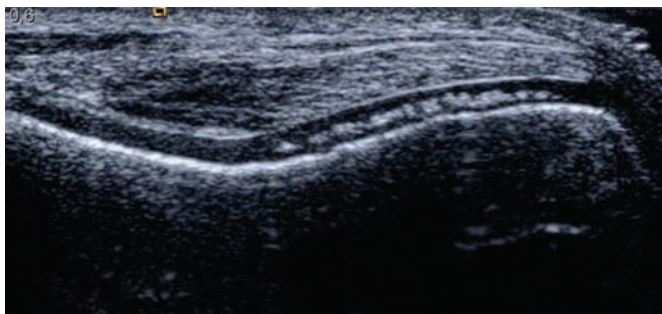


**Figure 3** Synovial fluid calcium pyrophosphate crystals (phase contrast, 1000 $\times$ ).



**Figure 4** Radiographic chondrocalcinosis of hyaline cartilage and fibrocartilage at the knee, occurring as an isolated phenomenon in an otherwise normal joint (above) and in association with changes (marginal osteophyte, medial compartment narrowing) of osteoarthritis (below).

## Recommendations



**Figure 5** Ultrasound of knee showing hyperechogenicity of the midzone of femoral hyaline cartilage, consistent with chondrocalcinosis due to calcium pyrophosphate (CPP) crystals.

small study may not be generalisable and further studies are required.

There are several possible reasons for discordance between CC and SF crystal positivity including: lack of specificity of CC for CPPD (basic calcium phosphates may also cause this); low sensitivity of radiographs for detecting CC; possible greater difficulty in identifying small numbers of SF CPP crystals in situations other than acute CPP crystal synovitis (especially when there is isolated CC and no cartilage fibrillation to encourage crystal shedding); and reduced ability to identify CC when there is significant cartilage loss. Also being small and weakly, or non-birefringent,<sup>61</sup> CPP crystals may be underdetected.

### Proposition 9

Case-control studies have examined the usefulness of ultrasonography (US) in detecting calcification in knees (figure 5),<sup>62 63</sup> wrists and shoulders.<sup>63</sup> US of the knee appears sensitive (0.87, 95% CI 0.69 to 1.04) and specific (0.96, 95% CI 0.90 to 1.03) for detection of SF CPP crystals.<sup>62</sup> Positive US findings may strongly suggest the diagnosis of CPPD (LR=24.2, 95% CI 3.51 to 168.01). Given a positive US result, the likelihood of a patient having SF CPP crystals in the same joint (eg, knee) in the UK population, for example, would be 65%. Suitability of US to detect calcification varies between sites (table 2) and it is insensitive for deep structures (eg, spine). One direct comparison showed US to be more sensitive (100%) than x-rays (82%) in identifying CPPD.<sup>63</sup> However, although US seems a promising technique for crystal identification the few published studies emanate from just a few centres and further studies are required.

## Comorbidities and risk factors

### Proposition 10

One study in a tertiary centre retrospectively reviewed all cases with crystal positive SF samples identified over a 7-year period. Of 265 positive samples, 183 (69.0%) contained MSU crystals, 81 (30.6%) contained CPP crystals and 1 (0.4%) contained both. Four (1.5%) also had positive cultures; of these, three were from joints with CPP crystals.<sup>64</sup>

### Proposition 11

As discussed,<sup>3 4</sup> OA and ageing are major risk factors/associations for CPPD. There are common risk factors for OA and CPPD (eg, ageing, joint injury) but OA cartilage also directly encourages deposition of calcium crystals (basic calcium phosphates as well as CPP).<sup>65</sup> Conversely, CPPD could be a primary factor that causes, or amplifies joint damage in OA.<sup>65</sup> Whether gender influences CPPD remains controversial, but pooling of eight cross sectional/case-control studies yields a non-significant association (OR=0.89, 95% CI 0.58 to 1.38). Although body

mass index is a major risk factor for OA, there is no evidence of association with CPPD (table 3).

Previous joint injury may predispose to CPPD. One retrospective cohort study found the risk of CC in postmeniscectomy knees to be five times greater (OR=5.00, 95% CI 1.77 to 14.11) than in contralateral unoperated knees<sup>32</sup> (table 3).

Several studies have investigated the association between CPPD and primary hyperparathyroidism, of which five provided data to summarise the association.<sup>40 66-69</sup> Patients with hyperparathyroidism are three times more likely to have CPPD than controls (OR=3.03, 95% CI 1.15 to 8.02) (table 3).

Evidence for the association between haemochromatosis and CPPD is relatively sparse. One hospital case-control study found no significant association (OR=1.04, 95% CI 0.42 to 2.60), although patients with haemochromatosis developed CPPD at a younger age (<60) than those without haemochromatosis (OR=3.05, 95% CI 1.12 to 8.33).<sup>67</sup> In a study of 178 patients with untreated haemochromatosis (mean age 50 years) prevalence of CC was 30% and the number of joints with CC correlated positively with age, ferritin level and serum parathyroid hormone 44-68 pg/ml.<sup>70</sup> In another hospital series of 54 patients with idiopathic haemochromatosis, (mean age 56, range 39-74 years), 31 (57%) had arthropathy which significantly associated with CC (OR=6.81, 95% CI 2.02 to 22.95)<sup>71</sup>.

Hypomagnesaemia associates with increased risk of CPPD. A case control study of 72 patients with chronic intestinal failure and 72 age and gender matched controls demonstrated increased risk of CC (OR=13.5, 95% CI 2.76 to 127.3) in those with intestinal failure.<sup>72</sup> Diuretic use was a risk factor for CC in one community study<sup>18</sup> and this might be explained by diuretic-induced hypomagnesaemia (table 3). Case reports and hospital series support associations with rare diseases such as hypophosphatasia.<sup>73 74</sup>

Although relatively uncommon, screening for hyperparathyroidism, haemochromatosis and hypomagnesaemia may be considered in patients with CPPD, and patients with these conditions are a high-risk population for CPPD.

Although rare families with young-onset polyarticular CPPD and monogenic inheritance pattern are recognised,<sup>75</sup> current evidence does not support familial aggregation for patients with common CC (OR=1.10, 95% CI 0.58 to 2.08).<sup>41 76</sup> However, a positive family history may relate to an earlier onset of CPPD.<sup>76</sup>

## Future research agenda

After four Delphi rounds five propositions were agreed.

1. Whether there are significant differences (eg, in symptoms, joint distribution, clinical outcomes) between OA with and without CPPD requires further study.
2. Clinical studies (using crystal identification as the gold standard for diagnosis) are required to better define the spectrum of CPPD and its possible clinical subsets.
3. An optimal protocol (including training) and agreed European standard for the identification of CPP crystals in SF needs to be established.
4. The validity of different imaging techniques for the diagnosis of CPPD should be evaluated, leading to recommendations about their application in routine care.
5. Further studies are required to determine whether correction of associated metabolic disease (eg, primary hyperparathyroidism, haemochromatosis) influences progression and outcome of CPPD associated arthropathy.

## DISCUSSION

A large number of terms are used for CPPD and its clinical phenotypes. However, the plethora of 'pseudo' syndromes and inconsistent use of terms such as pseudogout and CC often cause confusion. The EULAR CPPD Task Force therefore suggests 'calcium pyrophosphate deposition' (CPPD) as the umbrella term for all instances of CPP crystal deposition. Under this umbrella, asymptomatic CPPD, OA with CPPD, acute CPP crystal arthritis and chronic CPP crystal inflammatory arthritis are included. It was felt that terms prefixed by 'pseudo' should be abandoned because they do not specify the causative crystal, are probably not discrete clinical subsets, are a source of potential confusion for patients, and intimate that CPP crystals are of secondary importance and interest compared to sodium urate. The term chondrocalcinosis is retained for cartilage calcification, which is most commonly due to CPPD. It is appreciated that introduction of new terminology may prove inconvenient in the short term, but would be beneficial in the long term for research, education and clinical practice.

There are several limitations to this project. Firstly, we established expert consensus prior to systematic review of research evidence. While this approach addresses clinically relevant questions, it is not comprehensive. Secondly, the recommendations are not intended to classify CPPD for research purposes but to provide recommendations for clinical diagnosis. Thirdly, clinical studies used different gold standards for diagnosis, making comparison between diagnostic tests difficult. Furthermore, research evidence for diagnosis of CPPD is generally sparse and of poor quality. We therefore provided a suggested future research agenda to encourage expansion of the evidence base.

**Acknowledgements** We would like to thank the European League Against Rheumatism for financial support, Helen Richardson for coordination, Joanna Ramowski and Amanda Moody for assistance with the literature search and data collection and Daniel McWilliams for help in data analysis.

**Funding** Financial support was received from the European League Against Rheumatism.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Competing interests** None.

## REFERENCES

- Gordon TP, Smith M, Ebert B, *et al*. Articular chondrocalcinosis in a hospital population: an Australian experience. *Aust N Z J Med* 1984;**14**:655–9.
- Salaffi F, De Angelis R, Grassi W. Prevalence of musculoskeletal conditions in an Italian population sample: results of a regional community-based study. I. The MAPPING study. *Clin Exp Rheumatol* 2005;**23**:819–28.
- Doherty M, Dieppe P. Crystal deposition disease in the elderly. *Clin Rheum Dis* 1986;**12**:97–116.
- Ryan LM, McCarty DJ. *Calcium pyrophosphate crystal deposition disease, pseudogout, and articular chondrocalcinosis*. In: Koopman W, ed. *Arthritis and Allied Conditions: A textbook of Rheumatology*. Baltimore, MD: Williams and Wilkins 1997:2103–26.
- Hollander JL, Jessar RA, McCarty DJ. Synovial analysis: an aid in arthritis diagnosis. *Bull Rheum Dis* 1961;**12**:263–4.
- Kohn NN, Hughes RE, McCarty DJ Jr, *et al*. The significance of calcium phosphate crystals in the synovial fluid of arthritic patients: the "pseudogout syndrome". II. Identification of crystals. *Ann Intern Med* 1962;**56**:738–45.
- McCarty DJ. Calcium pyrophosphate dihydrate crystal deposition disease--1975. [Review] [62 refs]. *Arthritis Rheum* 1976;**19**:Suppl-85.
- Neame R, Doherty M. Calcium Pyrophosphate Dihydrate Crystal-associated Arthropathy. In: Hochberg MC, ed. *Rheumatology*, 4th Edition. New York: Elsevier; 2008: 1847-59.
- Zhang W, Doherty M, Pascual E, *et al*. EULAR evidence based recommendations for gout. Part I: Diagnosis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). *Ann Rheum Dis* 2006;**65**:1301–11.
- Zhang W, Doherty M, Bardin T, *et al*. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). *Ann Rheum Dis* 2006;**65**:1312–24.
- Dougados M, Betteridge N, Burmester GR, *et al*. EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees. *Ann Rheum Dis* 2004;**63**:1172–6.
- Jones J, Hunter D. Consensus methods for medical and health services research. *BMJ* 1995;**311**:376–80.
- Zhang W, Doherty M, Arden N, *et al*. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). *Ann Rheum Dis* 2005;**64**:669–81.
- Roddy E, Zhang W, Doherty M, *et al*. Evidence-based clinical guidelines: a new system to better determine true strength of recommendation. *J Eval Clin Pract* 2006;**12**:347–52.
- Whitehead A, Whitehead J. A general parametric approach to the meta-analysis of randomized clinical trials. *Stat Med* 1991;**10**:1665–77.
- Ogata M. [A clinical study of calcium pyrophosphate dihydrate crystal deposition disease]. *Nippon Seikeigeka Gakkai Zasshi* 1985;**59**:819–34.
- Felson DT, Anderson JJ, Naimark A, *et al*. The prevalence of chondrocalcinosis in the elderly and its association with knee osteoarthritis: the Framingham Study. *J Rheumatol* 1989;**16**:1241–5.
- Neame RL, Carr AJ, Muir K, *et al*. UK community prevalence of knee chondrocalcinosis: evidence that correlation with osteoarthritis is through a shared association with osteophyte. *Ann Rheum Dis* 2003;**62**:513–8.
- Neogi T, Nevitt M, Niu J, *et al*. Lack of association between chondrocalcinosis and increased risk of cartilage loss in knees with osteoarthritis: results of two prospective longitudinal magnetic resonance imaging studies. *Arthritis Rheum* 2006;**54**:1822–8.
- Riestra JL, Sánchez A, Rodríguez-Valverde V, *et al*. Roentgenographic features of the arthropathy associated with CPPD crystal deposition disease. A comparative study with primary osteoarthritis. *J Rheumatol* 1985;**12**:1154–8.
- Schouten JS, van den Ouweland FA, Valkenburg HA. A 12 year follow up study in the general population on prognostic factors of cartilage loss in osteoarthritis of the knee. *Ann Rheum Dis* 1992;**51**:932–7.
- Resnick D, Niwayama G, Goergen TG, *et al*. Clinical, radiographic and pathologic abnormalities in calcium pyrophosphate dihydrate deposition disease (CPPD): pseudogout. *Radiology* 1977;**122**:1–15.
- Steinbach LS, Resnick D. Calcium pyrophosphate dihydrate crystal deposition disease revisited. *Radiology* 1996;**200**:1–9.
- Yang BY, Sartoris DJ, Djukic S, *et al*. Distribution of calcification in the triangular fibrocartilage region in 181 patients with calcium pyrophosphate dihydrate crystal deposition disease. *Radiology* 1995;**196**:547–50.
- Yang BY, Sartoris DJ, Resnick D, *et al*. Calcium pyrophosphate dihydrate crystal deposition disease: frequency of tendon calcification about the knee. *J Rheumatol* 1996;**23**:883–8.
- Canhão H, Fonseca JE, Leandro MJ, *et al*. Cross-sectional study of 50 patients with calcium pyrophosphate dihydrate crystal arthropathy. *Clin Rheumatol* 2001;**20**:119–22.
- Gerster JC, Lagier R, Boivin G. Achilles tendinitis associated with chondrocalcinosis. *J Rheumatol* 1980;**7**:82–8.
- Gerster JC, Lagier R. Upper limb pyrophosphate tenosynovitis outside the carpal tunnel. *Ann Rheum Dis* 1989;**48**:689–91.
- Jean CG, René L, Georges B. Olecranon bursitis related to calcium pyrophosphate dihydrate crystal deposition disease. Clinical and pathologic study. *Arthritis Rheum* 1982;**25**:989–96.
- Ishida T, Dorfman HD, Bullough PG. Tophaceous pseudogout (tumoral calcium pyrophosphate dihydrate crystal deposition disease). *Hum Pathol* 1995;**26**:587–93.
- Salcman M, Khan A, Symonds DA. Calcium pyrophosphate arthropathy of the spine: case report and review of the literature. *Neurosurgery* 1994;**34**:915–8; discussion 918.
- Doherty M, Watt I, Dieppe PA. Localised chondrocalcinosis in post-meniscectomy knees. *Lancet* 1982;**1**:1207–10.
- Arveu I, Strutynsky C, Camus A, *et al*. Acute articular chondrocalcinosis episodes in the elderly subject. On a prospective evaluation in short-stay geriatric care and a literature review. *Revue Geriatr* 1999;**24**:63–8.
- Bergström G, Bjelle A, Sundh V, *et al*. Joint disorders at ages 70, 75 and 79 years—a cross-sectional comparison. *Br J Rheumatol* 1986;**25**:333–41.
- Louthrenoo W, Sukitawut W. Calcium pyrophosphate dihydrate crystal deposition: a clinical and laboratory analysis of 91 Thai patients. *J Med Assoc Thai* 1999;**82**:569–76.
- Wilkins E, Dieppe P, Maddison P, *et al*. Osteoarthritis and articular chondrocalcinosis in the elderly. *Ann Rheum Dis* 1983;**42**:280–4.
- Bergström G, Bjelle A, Sorensen LB, *et al*. Prevalence of rheumatoid arthritis, osteoarthritis, chondrocalcinosis and gouty arthritis at age 79. *J Rheumatol* 1986;**13**:527–34.

## Recommendations

38. **Doherty M**, Dieppe P, Watt I. Low incidence of calcium pyrophosphate dihydrate crystal deposition in rheumatoid arthritis, with modification of radiographic features in coexistent disease. *Arthritis Rheum* 1984;**27**:1002–9.
39. **Sanmartí R**, Pañella D, Brancós MA, *et al*. Prevalence of articular chondrocalcinosis in elderly subjects in a rural area of Catalonia. *Ann Rheum Dis* 1993;**52**:418–22.
40. **Yashiro T**, Okamoto T, Tanaka R, *et al*. Prevalence of chondrocalcinosis in patients with primary hyperparathyroidism in Japan. *Endocrinol Jpn* 1991;**38**:457–64.
41. **Zhang W**, Neame R, Doherty S, *et al*. Relative risk of knee chondrocalcinosis in siblings of index cases with pyrophosphate arthropathy. *Ann Rheum Dis* 2004;**63**:969–73.
42. **Reginato AJ**, Hollander JL, Martinez V, *et al*. Familial chondrocalcinosis in the Chiloe Islands, Chile. *Ann Rheum Dis* 1975;**34**:260–8.
43. **Zhang Y**, Johnson K, Russell RG, *et al*. Association of sporadic chondrocalcinosis with a -4-basepair G-to-A transition in the 5'-untranslated region of ANKH that promotes enhanced expression of ANKH protein and excess generation of extracellular inorganic pyrophosphate. *Arthritis Rheum* 2005;**52**:1110–7.
44. **Utsinger PD**, Resnick D, Zvaifler NJ. Wrist arthropathy in calcium pyrophosphate dihydrate deposition disease. *Arthritis Rheum* 1975;**18**:485–91.
45. **Crúz J**, Aviña-Zubieta A, Martínez de la Escalera G, *et al*. Molecular heterogeneity of prolactin in the plasma of patients with systemic lupus erythematosus. *Arthritis Rheum* 2001;**44**:1331–5.
46. **Andrianakos AA**, Kontelis LK, Karamitsos DG, *et al*. Prevalence of symptomatic knee, hand, and hip osteoarthritis in Greece. The ESORDIG study. *J Rheumatol* 2006;**33**:2507–13.
47. **Felson DT**, Lawrence RC, Dieppe PA, *et al*. Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med* 2000;**133**:635–46.
48. **Oliveria SA**, Felson DT, Reed JI, *et al*. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. *Arthritis Rheum* 1995;**38**:1134–41.
49. **Al-Arfaj AS**. The relationship between chondrocalcinosis and osteoarthritis in Saudi Arabia. *Clin Rheumatol* 2002;**21**:493–6.
50. **Menkes CJ**, Decraemere W, Postel M, *et al*. Chondrocalcinosis and rapid destruction of the hip. *J Rheumatol* 1985;**12**:130–3.
51. **Sanmartí R**, Kanterewicz E, Pladevall M, *et al*. Analysis of the association between chondrocalcinosis and osteoarthritis: a community based study. *Ann Rheum Dis* 1996;**55**:30–3.
52. **Stucki G**, Hardegger D, Böhm U, *et al*. Degeneration of the scaphoid-trapezium joint: a useful finding to differentiate calcium pyrophosphate deposition disease from osteoarthritis. *Clin Rheumatol* 1999;**18**:232–7.
53. **Ledingham J**, Regan M, Jones A, *et al*. Factors affecting radiographic progression of knee osteoarthritis. *Ann Rheum Dis* 1995;**54**:53–8.
54. **Bourqui M**, Vischer TL, Stasse P, *et al*. Pyrophosphate arthropathy in the carpal and metacarpophalangeal joints. *Ann Rheum Dis* 1983;**42**:626–30.
55. **Hansen SE**, Herning M. A comparative study of radiographic changes in knee joints in chondrocalcinosis, osteoarthritis and rheumatoid arthritis. *Scand J Rheumatol* 1984;**13**:85–92.
56. **Brasseur JP**, Huaux JP, Devogelaer JP, *et al*. Articular chondrocalcinosis in seropositive rheumatoid arthritis. Comparison with a control group. *J Rheumatol* 1987;**14**:40–1.
57. **McCarty DJ**, Kohn NN, Faires JS. The significance of calcium phosphate crystals in the synovial fluid of arthritic patients: the pseudogout syndrome. I. Clinical aspects. *Ann Intern Med* 1962;**56**:711–37.
58. **Swan A**, Amer H, Dieppe P. The value of synovial fluid assays in the diagnosis of joint disease: a literature survey. *Ann Rheum Dis* 2002;**61**:493–8.
59. **Lumbreras B**, Pascual E, Frasquet J, *et al*. Analysis for crystals in synovial fluid: training of the analysts results in high consistency. *Ann Rheum Dis* 2005;**64**:612–5.
60. **Martínez Sanchis A**, Pascual E. Intracellular and extracellular CPPD crystals are a regular feature in synovial fluid from uninfamed joints of patients with CPPD related arthropathy. *Ann Rheum Dis* 2005;**64**:1769–72.
61. **Ivorra J**, Rosas J, Pascual E. Most calcium pyrophosphate crystals appear as non-birefringent. *Ann Rheum Dis* 1999;**58**:582–4.
62. **Filippou G**, Frediani B, Gallo A, *et al*. A "new" technique for the diagnosis of chondrocalcinosis of the knee: sensitivity and specificity of high-frequency ultrasonography. *Ann Rheum Dis* 2007;**66**:1126–8.
63. **Frediani B**, Filippou G, Falsetti P, *et al*. Diagnosis of calcium pyrophosphate dihydrate crystal deposition disease: ultrasonographic criteria proposed. *Ann Rheum Dis* 2005;**64**:638–40.
64. **Shah K**, Spear J, Nathanson LA, *et al*. Does the presence of crystal arthritis rule out septic arthritis? *J Emerg Med* 2007;**32**:23–6.
65. **Dieppe P**, Doherty M. Which comes first: Crystals or osteoarthritis? *J Rheumatol* 1983;**10**:42–3.
66. **Alexander GM**, Dieppe PA, Doherty M, *et al*. Pyrophosphate arthropathy: a study of metabolic associations and laboratory data. *Ann Rheum Dis* 1982;**41**:377–81.
67. **Huauux JP**, Geubel A, Koch MC, *et al*. The arthritis of hemochromatosis. A review of 25 cases with special reference to chondrocalcinosis, and a comparison with patients with primary hyperparathyroidism and controls. *Clin Rheumatol* 1986;**5**:317–24.
68. **Pritchard MH**, Jessop JD. Chondrocalcinosis in primary hyperparathyroidism. Influence of age, metabolic bone disease, and parathyroidectomy. *Ann Rheum Dis* 1977;**36**:146–51.
69. **Rynes RI**, Merzig EG. Calcium pyrophosphate crystal deposition disease and hyperparathyroidism: a controlled, prospective study. *J Rheumatol* 1978;**5**:460–8.
70. **Pawlotsky Y**, Le Dantec P, Moirand R, *et al*. Elevated parathyroid hormone 44-68 and osteoarticular changes in patients with genetic hemochromatosis. *Arthritis Rheum* 1999;**42**:799–806.
71. **Dymock IW**, Hamilton EB, Laws JW, *et al*. Arthropathy of haemochromatosis. Clinical and radiological analysis of 63 patients with iron overload. *Ann Rheum Dis* 1970;**29**:469–76.
72. **Richette P**, Ayoub G, Lahalle S, *et al*. Hypomagnesemia associated with chondrocalcinosis: a cross-sectional study. *Arthritis Rheum* 2007;**57**:1496–501.
73. **Jones AC**, Chuck AJ, Arie EA, *et al*. Diseases associated with calcium pyrophosphate deposition disease. *Semin Arthritis Rheum* 1992;**22**:188–202.
74. **Richette P**, Bardin T, Doherty M. An update on the epidemiology of calcium pyrophosphate dihydrate crystal deposition disease. *Rheumatology (Oxford)* 2009;**48**:711–5.
75. **Netter P**, Bardin T, Bianchi A, *et al*. The ANKH gene and familial calcium pyrophosphate dihydrate deposition disease. *Joint Bone Spine* 2004;**71**:365–8.
76. **Fernandez Dapica MP**, Gómez-Reino JJ. Familial chondrocalcinosis in the Spanish population. *J Rheumatol* 1986;**13**:631–3.
77. **Viriyaevkul P**, Wilairatana V, Tanavalee A, *et al*. Comparison of characteristics of patients with and without calcium pyrophosphate dihydrate crystal deposition disease who underwent total knee replacement surgery for osteoarthritis. *Osteoarthritis Cartil* 2007;**15**:232–5.
78. **Falsetti P**, Frediani B, Acciai C, *et al*. Ultrasonographic study of Achilles tendon and plantar fascia in chondrocalcinosis. *J Rheumatol* 2004;**31**:2242–50.
79. **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.
80. **Sanmartí R**, Serrarols M, Galinsoga A, *et al*. [Diseases associated with articular chondrocalcinosis: an analysis of a series of 95 cases]. *Med Clin (Barc)* 1993;**101**:294–7.



## European League Against Rheumatism recommendations for calcium pyrophosphate deposition. Part I: terminology and diagnosis

W Zhang, M Doherty, T Bardin, et al.

*Ann Rheum Dis* 2011 70: 563-570 originally published online January 7, 2011

doi: 10.1136/ard.2010.139105

---

Updated information and services can be found at:

<http://ard.bmj.com/content/70/4/563.full.html>

---

*These include:*

### References

This article cites 77 articles, 28 of which can be accessed free at:

<http://ard.bmj.com/content/70/4/563.full.html#ref-list-1>

Article cited in:

<http://ard.bmj.com/content/70/4/563.full.html#related-urls>

### Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

---

### Topic Collections

Articles on similar topics can be found in the following collections

[Degenerative joint disease](#) (3939 articles)  
[Musculoskeletal syndromes](#) (4213 articles)  
[Clinical diagnostic tests](#) (1113 articles)  
[Osteoarthritis](#) (813 articles)  
[Radiology](#) (981 articles)  
[Radiology \(diagnostics\)](#) (673 articles)

---

### Notes

---

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>