

**Title:** Comparison of outcomes after UKR in patients with and without chondrocalcinosis – a matched cohort study

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**Keywords:** unicompartmental knee replacement, chondrocalcinosis, patient reported outcome; implant survival

**Level of Evidence:** Level III, case control study

1 **Comparison of outcomes after UKR in patients with and without chondrocalcinosis – a**  
2 **matched cohort study.**

3

4 **Abstract**

5 Chondrocalcinosis in the knee results from deposition of calcium crystals in the synovium,  
6 cartilage and meniscus. Calcium pyrophosphate crystals are the most common and can be  
7 associated with an inflammatory arthritis and in some cases aggressive joint destruction.

8 This study reports outcome of a consecutive series of patients with end-stage medial  
9 compartment arthritis and chondrocalcinosis, 88 radiological (R-CCK), 67 histological (H-  
10 CCK), matched to a cohort of patients without evidence of chondrocalcinosis (each CCK  
11 patient matched with two controls), and treated with Oxford unicompartmental knee  
12 replacement (UKR), between 1998 and 2008.

13 The mean follow up was 10 years. The mean Oxford Knee Score (OKS) at final follow up  
14 was 42.5, 40.8 and 40.8 in H-CCK, R-CCK and control groups respectively. The change in  
15 OKS compared to preoperative OKS was 20.7 in H-CCK, 17.9 in R-CCK and 15.2 in the  
16 control group. The change was significantly higher in H-CCK than control but was not  
17 significantly different in R-CCK. The 10 year survival was 96% in R-CCK, 86% in H-CCK  
18 and 98% in control. Although, the survival in H-CCK was significantly worse than control  
19 (HR 5.63, 95% CI 1.17-27.19, p=0.03); only one of the six failures in H-CCK was due to  
20 disease progression.

21 The presence of R-CCK does not influence the outcome of UKR. In contrast, H-CCK, which  
22 may represent pyrophosphate related arthritis (pseudogout), is associated with significantly  
23 improved clinical outcomes, yet also a higher revision rate compared to controls.

24 In conclusion pre-operative radiological evidence of CCK should not be considered to be a  
25 contra-indication to UKR but the role of pre-operatively histological diagnosis by knee  
26 aspiration still needs to be defined.

27

## 28 **Introduction**

29 Osteoarthritis of knee is often associated with calcium crystal deposition [4]. These calcium  
30 crystals are either calcium pyrophosphate dihydrate (CPPD), dicalcium phosphate dihydrate  
31 or basic calcium phosphate (BCP), including partly carbonate-substituted hydroxyapatite,  
32 tricalcium phosphate, and octacalcium phosphate. The calcium crystals may be deposited in  
33 the articular cartilage, meniscus and/or synovium [3,5,6,9]. The European League Against  
34 Rheumatism (EULAR) has defined Chondrocalcinosis as cartilage calcification, identified by  
35 imaging or histological examination, which may not always be due to CPPD and may occur  
36 as an isolated finding in an apparently otherwise normal joint or coexist with structural  
37 changes resembling OA [14].

38 Calcium pyrophosphate Dihydrate (CPPD) associated arthritis (pseudogout) is the third most  
39 common inflammatory arthritis [14]. This type of arthritis can at times be an aggressive form  
40 leading to rapid destruction of the knee joint [3,6,11,9]. It has been hypothesised that UKR in  
41 such patients might be more likely to fail as a result of subsequent involvement of the other  
42 compartments [2].

43 As a result, UKR in the presence of chondrocalcinosis is controversial. Kozinn and Scott,  
44 amongst others, suggest that UKR is contra-indicated in the presence of radiographic  
45 evidence of chondrocalcinosis [1,8,12]. In contrast, others suggest that chondrocalcinosis  
46 should not be a contra-indication to UKR [7,10,13].

47 The aim of this study is to compare the outcomes of UKR in patients with radiographic or  
48 histological evidence of chondrocalcinosis with a matched cohort of patients without  
49 chondrocalcinosis. Our null hypothesis was that there was no difference in the clinical  
50 outcome and implant survival of UKR in knee arthritis patients with and without evidence of  
51 chondrocalcinosis.

52

### 53 **Materials and Methods**

54 Data was prospectively collected on 1013 cemented phase 3 medial Oxford UKR (Biomet,  
55 Swindon, United Kingdom) implanted between 1998 and 2008. All operations were  
56 performed by the standard minimally invasive surgical technique by the two senior authors  
57 (CAFD and DM). The patients were assessed clinically by an independent physiotherapist  
58 using the Oxford Knee Score (OKS). Complications encountered and any further surgery on  
59 the same knee (including revision) were also recorded. The patients who could not attend for  
60 clinical follow up were sent postal questionnaires (15% equally distributed between the three  
61 groups). Patients who did not return questionnaires were contacted by telephone and were  
62 asked whether the knee had been revised and completed the OKS over the phone (7% of the  
63 entire cohort equally distributed in all the three groups). The information regarding patients  
64 who had died was obtained from hospital notes, general practitioner records and relatives.

65 All preoperative knee radiographs (antero-posterior and lateral views) of patients were  
66 assessed regarding the presence of calcification within the soft tissues of the knee joint. Intra-  
67 operative samples from articular cartilage (two samples – one from femur and one from  
68 tibia), meniscus (entire excised meniscus) and synovium (which was attached to articular  
69 cartilage and/or to the meniscus) were sent for histology and assessed for the presence of

70 calcium pyrophosphate crystal deposition as BCP and other calcium crystals cannot be  
71 identified by light microscopy. The knees with calcification on radiographs or histology were  
72 grouped as CCK group. The CCK group was further subdivided into;

- 73 • R-CCK: Patients who had radiological evidence of calcification irrespective of  
74 histology
- 75 • H-CCK: Patients who had histological evidence of chondrocalcinosis irrespective of  
76 radiology

77 Each patient with chondrocalcinosis (diagnosed by histology or radiology or both) was  
78 matched to two controls on the basis of age, gender and follow up period. Matching was  
79 performed using an optimal matching algorithm; a computer based program which allows  
80 random matching of the cases to controls using the user-written 'optmatch2' command.

81 In all the cases, the control group consisted of patients without chondrocalcinosis by either  
82 definition. For each outcome (survival, post-operative OKS and OKS change,  $\Delta$ OKS)  
83 separate case-control comparisons were performed for chondrocalcinosis diagnosed on the  
84 basis of radiographs, histology or overall (i.e. these two groups combined).

85 The definition of failure in the survival analysis was all-cause revision, which included any  
86 operation involving the removal or exchange of an existing component or components, or  
87 supplementation of an additional component (e.g., the addition of a lateral UKR for lateral  
88 compartment disease progression). All bearing dislocations were considered to be revisions.  
89 Following matching, implant survival data were analysed using Cox regression. For the OKS,  
90 conditional logistic regression was used. This is a form of logistic regression which accounts  
91 for the matched nature of the sample. OKS were compared both in terms of the latest  
92 postoperative score and the change from preoperative scores ( $\Delta$ OKS).

93 All analyses were performed using Stata v.12.1 for Windows (Stata Corp., College Station,  
94 TX). Statistical significance was set at  $p < 0.05$ .

95

## 96 **Results**

97 123/1013 knees (12%) had either radiological (87 (9%) knees) or histological (67 (7%)  
98 knees) evidence of chondrocalcinosis. 31 (3%) knees had both histological and radiological  
99 chondrocalcinosis.

100 Each case of chondrocalcinosis was successfully matched to two controls. The baseline  
101 demographics of the matched groups are displayed in table 1.

102 Values for implant survival in each case-control comparison are displayed in table 2 and  
103 figure 1 and 2. The number at risk at ten years for each group were as follows: H-CCK 21  
104 cases, R-CCK 35 cases, and overall (H-CCK or R-CCK) 45 cases.

105 There was no significant difference in the survival of radiological chondrocalcinosis group as  
106 compared to the controls. For chondrocalcinosis diagnosed on the basis of histological  
107 examination, there is significantly inferior survival compared to control 5.80 (1.19-28.30),  
108  $p=0.03$ .

109  $\Delta$ OKS is significantly better in patients with chondrocalcinosis overall, and those diagnosed  
110 histologically (Table 3). For chondrocalcinosis diagnosed on radiographs alone, there is no  
111 significant difference in  $\Delta$ OKS between cases and controls.

112 9 out of 123 knees with chondrocalcinosis underwent revision. 6/ 67 knees ( 9%) were in the  
113 H-CCK group, 3/87 (3.4%) were in the R-CCK group and 2/31 (6.5%) with both histological

114 and radiographic evidence of chondrocalcinosis. 4/246 (1.6%) knees in the control group  
115 underwent a revision.

116 Of the six knees in the histological chondrocalcinosis group undergoing revision, one knee  
117 was revised for lateral compartment OA (after 9 years and 5 months).The cause of revision in  
118 other 5 knees with chondrocalcinosis was aseptic loosening in one knee at 8 years and 2  
119 months, bearing dislocation in 2 knees (one at 9 months and another at 5 and half years),  
120 persistent pain in one knee at 5 years and 7 months and lateral AVN at 9 months in one knee  
121 (Table 4). In the 87 knees with radiological chondrocalcinosis, 3 knees underwent revision  
122 one each for persistent pain at 5 years and 7 months, bearing dislocation at 18 months  
123 (bearing revised at 18 months and thereafter underwent a revision to total knee arthroplasty at  
124 7 years and 10 months after index OUKR) and avascular necrosis of lateral femoral condyle  
125 leading to secondary OA at 9 months.

126

## 127 **Discussion**

128 The most important finding of the present study was that there was no significant difference  
129 in survival between patients undergoing medial UKR with radiological chondrocalcinosis and  
130 controls without chondrocalcinosis. However, patients with histologically proven  
131 chondrocalcinosis (due to calcium pyrophosphate dihydrate crystal deposition) had a  
132 significantly worse survival at 10 years compared to controls without chondrocalcinosis. The  
133 clinical outcome, as assessed by the change in Oxford Knee Score , was significantly better in  
134 patients with histological chondrocalcinosis compared to controls without chondrocalcinosis,  
135 whereas there was no significant difference in clinical outcome between patients with  
136 radiological chondrocalcinosis and controls.

137 There appears to be a difference between radiological and histological chondrocalcinosis  
138 even though there is some overlap. When patients are being assessed for UKR the main  
139 investigation is radiology; histology is not normally available. Therefore as far as UKR  
140 contraindications are concerned, what matters is radiological CCK. This study has shown  
141 that the R-CCK does not influence the survival rate or the functional outcome of UKR. On  
142 this basis, radiological chondrocalcinosis should not be considered a contra-indication to  
143 UKR. This conclusion is the same as that of both Wood and Hernigou [13,7]. Study by  
144 Woods *et al.* included 20 knees with CCK and the mean follow up was relatively short (4  
145 years). Hernigou's study included 85 patients with primary diagnosis of CCK with another 63  
146 diagnosed (radiographic evidence) in the follow up period. The study did not find any  
147 difference in clinical outcome or implant survival between the CCK and non-CCK groups;  
148 although no attempt was made to differentiate between the histological and radiographic  
149 CCK.

150 Compared with controls without CCK, H-CCK had a significantly worse implant survival but  
151 significantly better functional outcome. Patients that had H-CCK had evidence of CPPD  
152 crystal deposition, which can be associated with an inflammatory arthritis. With an  
153 inflammatory arthritis a high failure rate due to disease progression in the retained  
154 compartment might occur. However, only one of the six failures were due to disease  
155 progression and the other five (pain, dislocation, loosening and AVN) were unlikely to be  
156 related to an inflammation. It is therefore not certain whether the higher failure rate seen in  
157 H-CCK is of any consequence. It is also difficult to know why the functional outcome is  
158 better with H-CCK. Further study is needed to determine if H-CCK is a problem and if it can  
159 be diagnosed pre-operatively, perhaps by polarised light microscopy examination of synovial  
160 fluid.



161 There are many strengths of this study. A large number of cases with CCK are followed up  
162 (mean 10 years) with regular assessments by an independent physiotherapist. In addition, in  
163 all the cases (including controls) histological samples of articular cartilage and synovium  
164 were sent for histological examination. Set criteria for histological diagnosis were used. The  
165 main limitations of the study were that the knee joint was not aspirated pre-operatively or  
166 intra-operatively to assess for presence / absence of birefringent crystals under polarised  
167 light. Histology can only determine whether there is deposition of calcium pyrophosphate  
168 crystals in articular tissue. Deposition of other calcium crystals cannot be assessed by light  
169 microscopy so R-CCK and H-CCK do not represent the same subject group. According to  
170 EULAR recommendations for terminology and diagnosis of CPDD, radiographic  
171 chondrocalcinosis supports the diagnosis of CPDD, but its absence does not exclude it [14].  
172 In CPPD deposition, calcifications may be absent on radiology and can be present on  
173 histological examination.

#### 174 **Conclusion**

175 Pre-operative radiological evidence of CCK should not be considered to be a contra-  
176 indication to UKR. However, the relevance of histological CCK, which is associated with a  
177 significantly higher revision rate but also significantly better patient reported functional  
178 outcomes, is still unclear, and the role of pre-operative histological diagnosis still needs to be  
179 defined.

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Figure 1

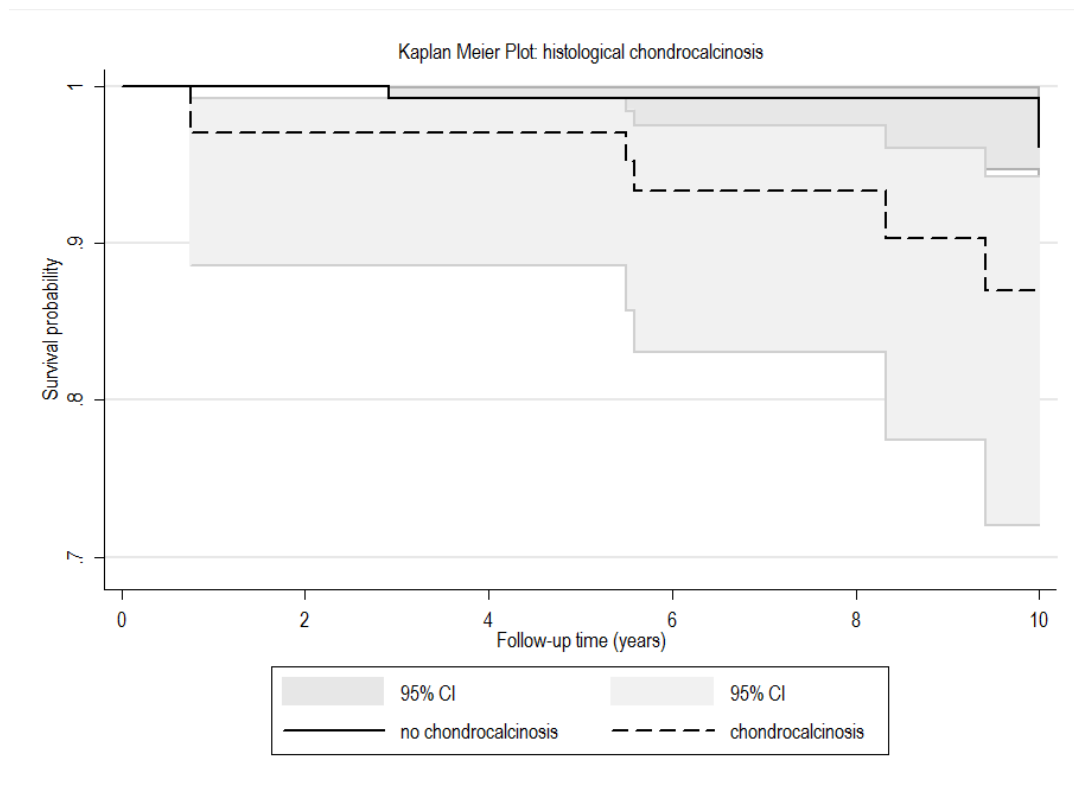


Figure 1: Kaplan Meier Plot of Survival Analysis of histological chondrocalcinosis

Figure 2

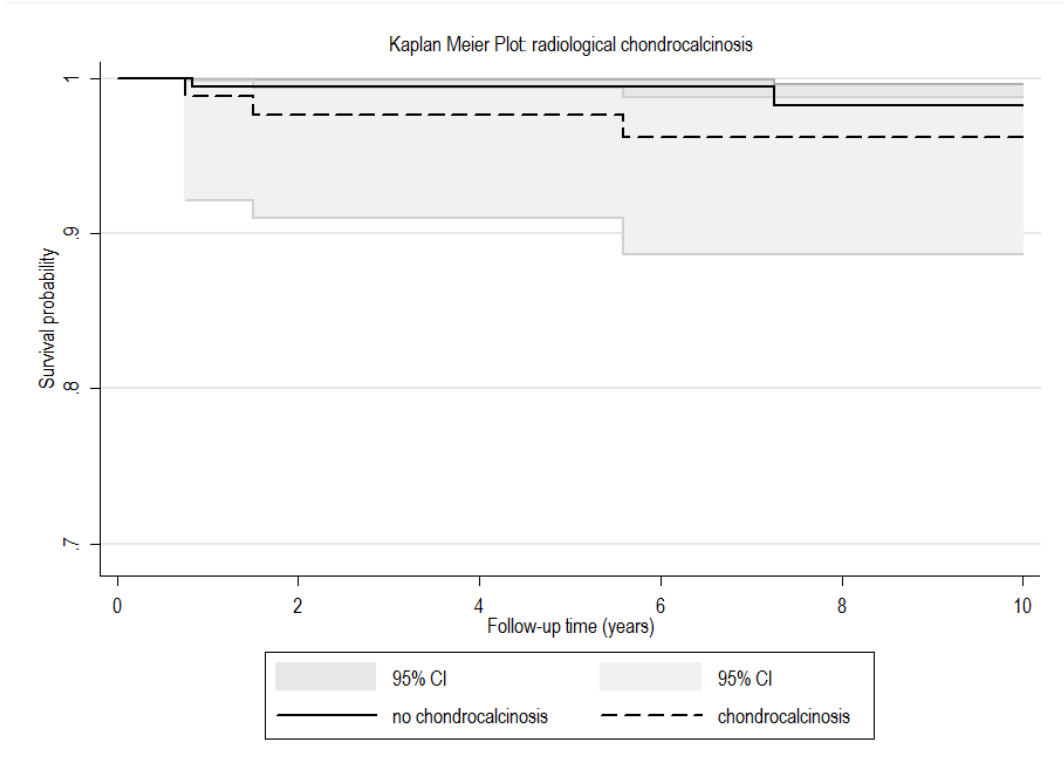


Figure 2: Kaplan Meier Plot of Survival Analysis of Radiological Chondrocalcinosis

Table 1: Baseline demographics of groups:

	Overall		Histological		Radiological	
	Cases	Controls	Cases	Controls	Cases	Controls
N	123	246	67	134	87	174
Mean age (SD)	69.8 (8.7)	69.2 (8.2)	70.1 (8.3)	70.8 (8.9)	68.7 (8.8)	68.2 (8.4)
Gender (% male)	144 (58.5)	72 (58.5)	42 (62.7)	84 (62.7)	51 (85.6)	102 (58.6)
Years Follow-up (SD)	10.0 (2.9)	9.2 (2.7)	10.1(2.9)	9.1 (2.6)	10.0 (3.0)	9.3 (2.8)

Table 2-Implant Survival using Cox regression

	Overall		Histological		Radiological	
	Cases	Controls	Cases	Controls	Cases	Controls
N	123	246	67	134	87	174
10 year survival	91.8 (82.6-96.2)	98.3 (94.3-99.5)	86.1 (69.6-94.0)	99.2 (94.7-99.9)	96.3 (92.4-99.6)	98.2 (92.4-99.9)
Hazard Ratio	3.33 (0.95-11.69) p=0.06		5.80 (1.19-28.30) p=0.03		2.91 (0.47-18.08) p=0.25	

Table 3-Mean Oxford Knee Scores (SD)

	Overall			Histological			Radiological		
	Cases	Controls	P	Cases	Controls	p	Cases	Controls	p
Pre-op	23.5 (9.2)	25.7 (8.5)	0.06	22.7 (8.6)	25.5 (8.6)	0.05	24.1 (9.9)	26.1 (8.5)	0.24
Latest	42.5 (7.4)	40.9 (8.1)	0.28	43.5 (5.9)	40.9 (8.1)	0.12	42.0 (8.0)	40.9 (8.1)	0.59
Change	19.0 (10.0)	15.2 (9.7)	<0.01	20.7 (9.2)	15.4 (9.8)	<0.01	17.9 (10.3)	14.8 (9.8)	0.12

Table 4-Causes of Revision

Cause	H-CCK	R-CCK	Control Group
Progression of OA in the Lateral Compartment	1	0	3
Pain	1	1	0
Bearing Dislocation	2	1	1
Infection	0	0	0
Aseptic Loosening	1	0	0
Avascular Necrosis (AVN) of lateral femoral condyle	1	1	0