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

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

Abstract

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

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

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

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

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

Introduction

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

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

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

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

Materials and Methods

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

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

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

- R-CCK: Patients who had radiological evidence of calcification irrespective of histology
- H-CCK: Patients who had histological evidence of chondrocalcinosis irrespective of radiology

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

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

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

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

Results

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

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

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

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

ΔOKS is significantly better in patients with chondrocalcinosis overall, and those diagnosed histologically (Table 3). For chondrocalcinosis diagnosed on radiographs alone, there is no significant difference in ΔOKS between cases and controls.

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

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

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

Discussion

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

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

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

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

Conclusion

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

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Figure 1

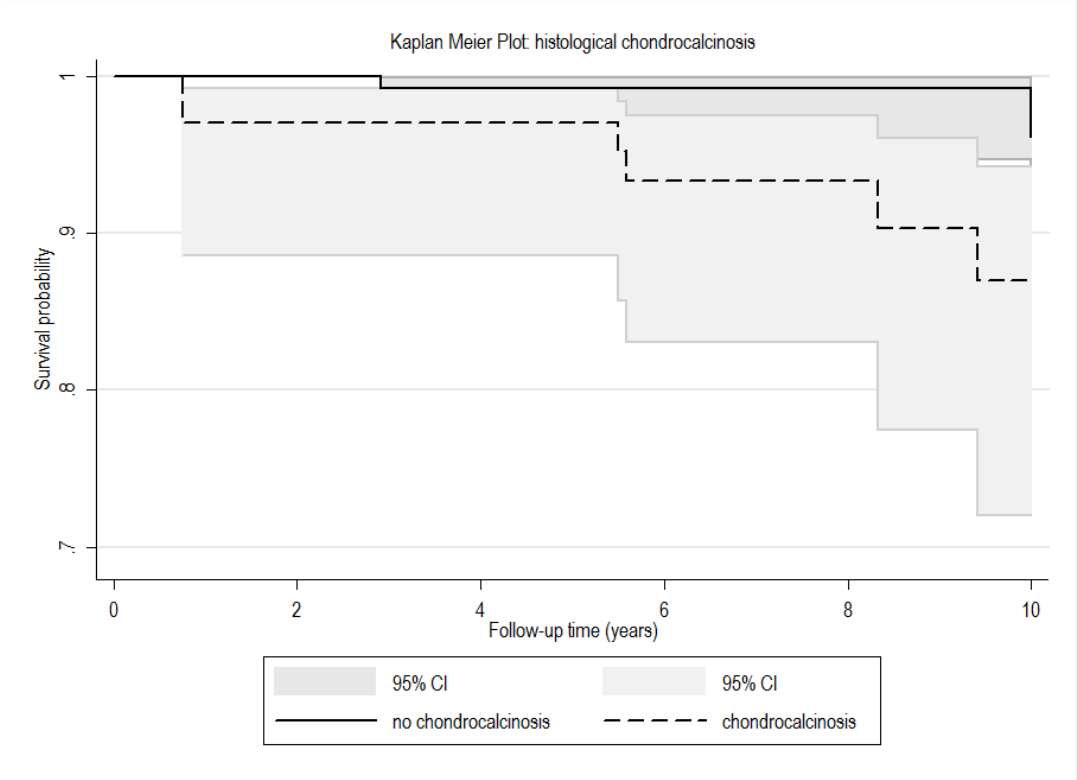

Figure 1: Kaplan Meier Plot of Survival Analysis of histological chondrocalcinosis

Figure 2

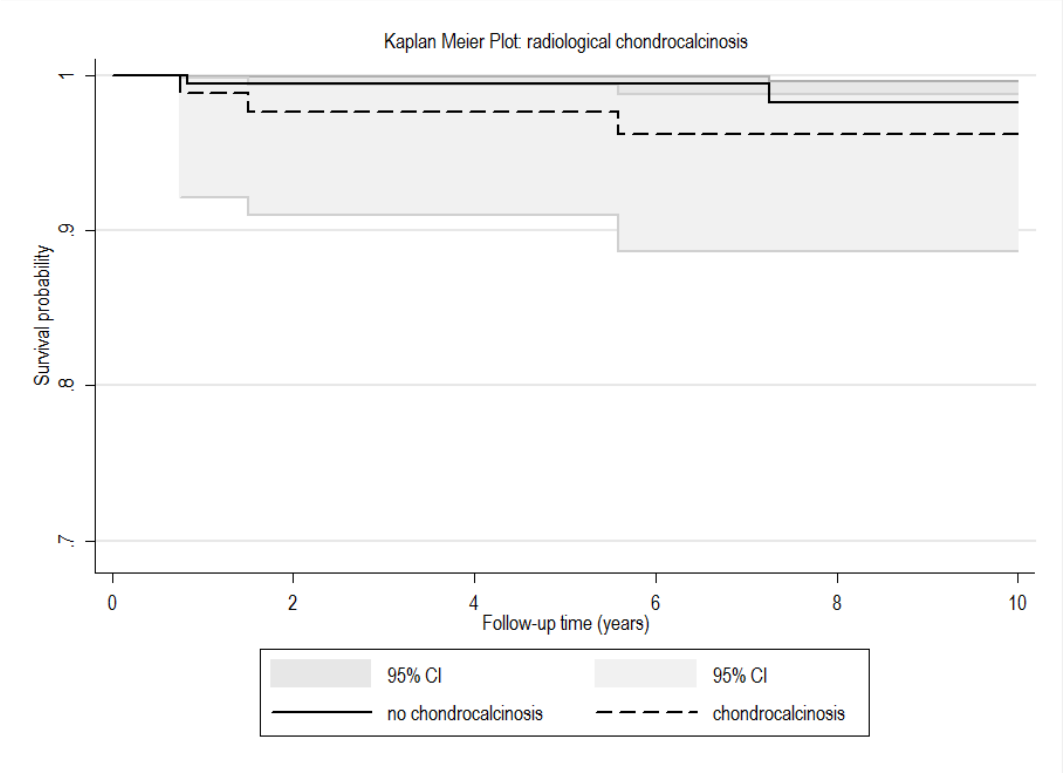

Figure 2: Kaplan Meier Plot of Survival Analysis of Radiological Chondrocalcinosis

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