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Reliability and diagnostic accuracy of radiography for the diagnosis of calcium pyrophosphate deposition: performance of the novel definitions developed by an international multidisciplinary working group

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Abstract

Objectives: To assess the reliability and diagnostic accuracy of new radiographic definitions for calcium pyrophosphate deposition (CPPD) identification, developed by an international multidisciplinary working group.

Methods: Patients with knee osteoarthritis scheduled for knee replacement were enrolled. Two radiologists and two rheumatologists assessed twice the images for presence/absence of CPPD on menisci, hyaline cartilage, tendons, joint capsule, synovial membrane, using the new definitions. In case of disagreement, a consensus decision was taken and considered for the assessment of diagnostic performance. Histological examination of specimens under compensated polarized light microscopy was the reference standard. Prevalence-adjusted bias-adjusted kappa (PABAK) was used to assess the reliability. Diagnostic performance statistics were calculated.

Results: Sixty-seven participants were enrolled for the reliability study. The inter-observer reliability was substantial in most of the assessed structures when considering all 4 readers (kappa range 0.59 – 0.90), substantial to almost perfect among radiologists (kappa range 0.70-0.91), and moderate to almost perfect among rheumatologists (kappa range 0.46 – 0.88). The intra-observer reliability was substantial to almost perfect for all the observers (kappa range 0.70 – 1). Fifty-one patients were enrolled for the accuracy study. Radiography demonstrated to be specific for CPPD (92%), but sensitivity remained low in all sites and in the overall diagnosis (54%).

Conclusion: The new imaging definitions of CPPD are highly specific against the gold standard of histological diagnosis; when described findings are present these definitions allow for a

definite diagnosis of CPPD, rather than other calcium-containing crystal depositions; instead a negative finding does not exclude the diagnosis.

Keywords: CPPD; X-ray; Imaging; Crystal-induced Arthritis; Osteoarthritis

Introduction

Calcium pyrophosphate deposition (CPPD) disease is the umbrella term used to describe all instances of calcium pyrophosphate (CPP) crystal deposition in tissues (1). It can present with heterogeneous phenotypes ranging from asymptomatic form to acute or chronic arthritis or can overlap with other rheumatic diseases (1), making the diagnosis challenging and raising questions about attribution of symptoms to CPPD vs. other arthropathies. CPPD disease appears to be the third most common form of inflammatory arthritis (2), its prevalence increases with ageing, and in selected populations may reach a prevalence of 13% when defined as radiographic chondrocalcinosis (3,4). However, due to the nature of the disease and the lack of a non-invasive reference test, the estimated prevalence is probably minimizing the real occurrence of the disease in the general population. Further, it is an understudied and underdiagnosed condition and there are still major unmet needs in this field, as its pathogenesis is not fully understood, validated classification criteria have not been published to date, specific and effective therapies are lacking as are validated and reliable imaging techniques that may provide an accurate diagnosis (3,5–7).

The definite diagnosis of CPPD required visualisation of CPP crystals (8) in synovial fluid analysis (SFA) (1). However, SFA presents some limitations as it is not always feasible in clinical practice, it is operator dependent, and it shows only 70% of sensitivity, meaning that approximately one-third of the patients could be missed (9–11).

For this reason, a series of advanced imaging modalities are under investigation for use in CPPD diagnosis such as ultrasound (US), computed tomography (CT), dual-energy CT (DECT) multi-energy/spectral photon-counting CT (SPCCT) and spectral photon-counting radiography, showing promising results (12–18). However, to date, the validation process to consider such

techniques as possible outcome instruments in CPPD is in progress. Among them, US has travelled the furthest and has been assessed for construct, content and criterion validity within the Outcome Measures in Rheumatology (OMERACT) US working group (12,13), but the need for specific training and the still not ubiquitous availability limit its use.

Radiography is still considered one of the most important diagnostic methods for detecting chondrocalcinosis (i.e., the presence of any calcium deposition within articular cartilage), given its widespread use, the low cost, and the long tradition. Further, a major advantage of radiography is that it provides an overview of the entire joint allowing assessment of differential diagnosis or coexisting diseases. However, there are very few studies that examine its diagnostic performance in CPPD (19), and there are no studies on its reliability, making this imaging technique not appropriate for use as an outcome measure and for clinical practice to differentiate from basic calcium phosphate (BCP) crystals.

The need to reconsider imaging techniques in CPPD as outcome measures is remarkably relevant given the current and ongoing development of the American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) CPPD classification criteria (20). In parallel to this project, an international working group including members of the ACR/EULAR CPPD Classification Criteria working group (nine rheumatologists and one musculoskeletal radiologist) and five external musculoskeletal radiologists, developed definitions of imaging features of CPPD on a variety of imaging modalities, including radiography (20). These definitions attempted to indicate characteristic features that differentiate CPP crystals deposits from other types of calcium crystals, in order to increase specificity for CPPD (19). While they were developed for the purposes of classification criteria for CPPD research, they may also have broader application for CPPD diagnosis.

The aim of this ancillary study (12) conducted by the CPPD subgroup of the OMERACT US working group, is to evaluate the reliability and the accuracy (criterion validity) of the new radiographic definitions for CPPD in the knee.

Patients and Methods

This study follows the design and methods of the previously published multicentre cross-sectional study for the validation of US in CPPD (13). Briefly, consecutive patients with knee osteoarthritis (OA) requiring total joint replacement were prospectively enrolled in 8 centres from Italy (22 patients – University of Siena and University of Turin), Spain (11 patients – Hospital Universitario Fundacion Jimenez Diaz, Madrid), Switzerland (10 patients – University of Lausanne), Mexico (8 patients – Instituto Nacional de Rehabilitacion, Mexico City), Romania (7 patients – Carol Davila University, Bucharest), USA (6 patients – North Valley Hospital, Whitefish, Montana) and France (3 patients – University of Montpellier), all the investigators of each contributing site were members of the OMERACT US in CPPD working group. Recruitment was developed competitively from January to September 2019. Patients with other inflammatory joint disease or unable to sign the informed consent were excluded. Radiographies of the knees were made before surgery. After knee replacement, both menisci and tibiofemoral hyaline cartilage (HC), the same used in the main study, were collected for histological examination. All participants provided written informed consent for participation in the study. This study was approved by the institutional ethics committee of the University of Ferrara (principal investigator site, study number 171190 approved on 17 December 2017) and subsequently by local ethics committees of all the participating centers.

Radiographic assessment

All patients underwent radiography of both knees maximum 6 months prior to surgery, in anterior-posterior weight-bearing and lateral views. Radiographic images were obtained using a standard protocol. For anterior-posterior view, right and left knees were imaged together on

14 x 17 inch film using a source-to-object distance of 72 inches with X-ray beam parallel to the ground. Files of the preoperative radiographs were saved in DICOM format, anonymised, retrieved, and read independently by two musculoskeletal radiologists with 16 and 15 years' experience in crystal arthropathies, one experienced rheumatologist with more than 30 years' experience in crystal arthropathies and one trainee rheumatologist with 4 years of experience, that received a specific training in CPP crystals detection on radiography. The radiologists worked on their workstations (CARESTREAM [v. 12.2; Carestream Health, Rochester, NY, USA] or SECTRA [v. 23.1; SecTra, Linköping, Sweden] picture archive and communication systems equipped with a mammography-certified medical monitor); while the two rheumatologists assessed the images on their personal computer equipped with at least a 24" high-definition display. For each knee the examiners evaluated the presence or the absence of CPP deposits using a dichotomic score, at the level of the medial and lateral menisci, tibiofemoral HC, quadriceps and patellar tendons, synovial membrane and joint capsule. The novel definitions developed by the international working group were used for the identification of CPPD (21). According to these definitions, CPPD appears as "linear or punctate opacities in the region of fibro- or hyaline articular cartilage/synovial membrane or joint capsule/within tendons or entheses that are distinct from denser, nummular radio-opaque deposits due to BCP deposition" (Table 1). The examiners were all asked to strictly apply the definitions in order to avoid any influence deriving by personal experience and were provided by a reference image atlas to minimize variability in assessing CPPD (22). Investigators were blinded to clinical and histological data of the patients.

Reliability

Each reader performed two evaluations of the DICOM files, the first one to assess the inter-reader agreement, and the second, 3 weeks after the first one, to calculate the intra-reader agreement. File order was different in the two rounds and the knee to score was clearly indicated in the scoring sheet. The inter-reader agreement was assessed among all 4 readers, among the 2 radiologists and the 2 rheumatologists.

Diagnostic accuracy

After the two rounds, in case of disagreement on the presence of CPPD a consensus decision was taken by the two radiologists after discussion of the case in a virtual platform, and that decision was used for the assessment of accuracy. CPPD diagnosis was based on histological examination of knee tissues. Histology provides a direct visualisation of crystals within the structures of interest allowing a comparison with what is seen in imaging in the same structures, while SFA (frequently used as reference standard in other studies) provides only indirect evidence of the presence of crystals, not allowing a direct correspondence with imaging. Moreover, according to the pathogenetic mechanism of CPPD disease, crystals are primarily formed in cartilage, and subsequently shed into the synovial space due to damage or cartilage degeneration, and this suggest the importance of using histology as the reference standard, because crystals could be detected in tissues specimens before they are released in synovial fluid (23). Accuracy assessment was carried out only at the level of menisci and HC of the knee as tendons, joint capsule and synovial membrane were not retrieved during surgery. The diagnostic accuracy study was conducted according to the Standards for Reporting Diagnostic accuracy (STARD) 2015 guidelines (24).

Histological examination

Both menisci and the femoral condyles of each patient were retrieved after knee replacement surgery, washed with phosphate-buffered saline or physiological saline solution to remove blood, put in a sterile container with a unique ID code and stored in a refrigerator at -80 °C. Then the samples were delivered in dry ice to the University of Padua, Italy or analyzed on site following the same protocol described previously in detail (13). Briefly, menisci were cut into 10 segments of approximately the same dimensions and scraped with a curette or a spatula. Femoral condyles were sectioned in 10 different regions and each section was scraped. The resulting material was placed directly in a slide rinsed with 70% Ethanol Solution and by a drop of water and was observed at 400x magnification using compensated polarized light microscopy. The observation was focused on the detection of CPP crystals by morphology and birefringence (Figure 1). Patients were considered positive for CPPD based on the presence of CPP crystals in at least one of their tissue specimens. Examiners were blinded to other findings.

Statistical analysis

Prevalence-adjusted bias-adjusted kappa (PABAK) was used to measure the agreement between the readers. The strength of agreement for kappa was interpreted according to Landis and Koch (25): kappa values from 0.01–0.20 are considered as poor to slight agreement, 0.21–0.40 as fair, 0.41– 0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement. Readers were asked to score as absence/presence and no indeterminate data were expected. In case of missing data in histology, the patient was excluded from the accuracy analysis.

To reach an expected kappa value of 0.85, with an expected confidence interval lower bound of 0.75, 4 readers and 67 patients were sufficient.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were calculated; these diagnostic indexes were calculated for all the knee structures analysed at histology, that is medial and lateral meniscus and tibiofemoral HC.

The sample size, calculated for an expected prevalence of CPPD in these patients of 50% (12), an expected sensitivity and specificity of 75% and 90% respectively, an accuracy of 18% and 95% confidence level, was 47 patients.

Statistical analyses were performed using Stata/SE v17.0 (StataCorp LLC).

Results

Reliability study

Sixty-seven patients with OA awaiting total knee replacement surgery were enrolled for the reliability study, 65% were female with a mean age of 71 years ± 8. One patient had grade 1 OA according to Kellgren-Lawrence scoring (26), 8 patients had grade 2, 31 patients grade 3, and 11 patients grade 4.

Inter-reader agreement of all 4 observers was substantial in most of the assessed structures, with a kappa of 0.70 at medial meniscus, 0.79 at lateral meniscus, 0.80 at quadriceps tendon, 0.90 at patellar tendon, 0.74 at joint capsule and 0.76 at synovial membrane; with the exception of the HC that presents only moderate reliability (kappa of 0.59). The overall evaluation of the knee joint proved to be moderately reliable with a kappa of 0.53 if all anatomical structures are included for assessment, and substantially reliable with a kappa of 0.61 when only menisci and HC are considered. According to specialty, inter-observer agreement was substantial to almost perfect in all the knee structures among radiologists, in particular with kappa values of 0.82 at medial meniscus, 0.76 at lateral meniscus, 0.70 at HC, 0.91 at quadriceps tendon, 0.88 at patellar tendon, 0.82 at joint capsule and 0.79 at synovial membrane; and are moderate to almost perfect among rheumatologists, with a kappa of 0.52 at medial meniscus, 0.79 at lateral meniscus, 0.46 at HC, 0.64 at quadriceps tendon, 0.88 at patellar tendon, 0.64 at joint capsule and 0.79 at synovial membrane.

Regarding the intra-reader kappa values, they were substantial or higher in all sites for all the observers; the kappa values range from 0.85 to 0.97 for the first radiologist, from 0.91 to 1 for the second radiologist, from 0.70 to 1 for the expert rheumatologist, and from 0.91 to 0.97 for the trainee rheumatologist.

Kappa values of the inter-reader and intra-reader agreement in the various sites of the knee and in the overall evaluation are indicated in Table 2.

Diagnostic accuracy study

Fifty-one patients of the 67 enrolled had complete data for the histological analysis and were enrolled for the accuracy study (63% were female with a mean age of 74 ± 8 years). Not all specimens were retrieved during surgery, hence 16/67 patients were excluded from the accuracy study. Table 3 and Figure 2 show the relationship between radiography and tissue analysis.

The prevalence of CPPD according to the reference standard (histological analysis) was 51%, with 26/51 patients positive in at least one of examined tissues at histology (Table 3). Twenty-five were positive at medial meniscus, 25 at lateral meniscus and 23 at tibiofemoral HC. Further, 21 were positive in both menisci and HC, 3 at medial and lateral meniscus, 1 at medial meniscus and HC and 1 at lateral meniscus and HC, and none was positive in only one structure.

Regarding radiography, 16/51 patients (31%) were positive for CPPD (at least one positive structure), 8 patients at medial meniscus, 11 at lateral meniscus and 13 at HC (Figure 2). Moreover, 5 patients were positive only in 1 structure (2 at lateral meniscus, 3 at HC), 6 in 2 structures (1 at medial and lateral menisci, 2 at medial meniscus and HC, and 3 at lateral meniscus and HC), and 5 patients were positive in all the 3 structures.

Using histology as the reference standard the overall accuracy of radiography was 67% for medial meniscus, 69% for lateral meniscus, 73% for HC and 73% considering all sites evaluated. Depending on the site, the sensitivity ranged from 32% to 48%, with an overall sensitivity of

54%; the overall specificity was 92% (from 93% to 100%), with an overall PPV of 88% and an overall NPV of 66% as shown in table 4.

Discussion

Why should we use radiography for detecting CPPD in 2022? This question is not easy to answer as, to date, the only available data on the utility of radiography in assessing CPPD are dealing with its diagnostic accuracy, that in a recent meta-analysis was estimated at 60% for the sensitivity and 96% for specificity (24). Undoubtedly, sensitivity values are quite low for an imaging technique especially if compared with advanced imaging such as US that in the same meta-analysis yielded pooled values of 81% for sensitivity and 90% for specificity. Further, US is harmless, can be performed directly by the rheumatologist during the visit, it can assess also inflammation and joint damage and finally it has been validated for all these uses by the OMERACT US working group (11,12,25). Nevertheless, radiography is still considered a milestone in the guidelines for CPPD diagnosis (1) and is used generally as the first line exam by most rheumatologists for assessing joints with pain and especially degenerative diseases. Radiography, indeed, is able to identify joint damage, provides a panoramic view of the joint, is widely available and cheap. But its main advantage is that the acquisition technique is standardised, made by trained personnel, while interpretation of findings is quite simple on the contrary of US that requires a long training both for acquiring the necessary skills for a correct scanning technique and for learning how to interpret the US findings.

Given these premises, an international working group including members of the ACR/EULAR CPPD Classification Criteria working group and external musculoskeletal radiologists developed specific definitions for identification of CPPD on radiography (21). Indeed, until now, the presence of calcifications in joints at radiography was defined as chondrocalcinosis, a Greek

term meaning the presence of calcium crystals in cartilage. Chondrocalcinosis however is not necessarily due to CPPD but also to other calcium crystals such as BCP (1,29). The international working group attempted to differentiate between CPPD and other calcium crystal deposition by describing specific characteristics of CPPD in contrast to BCP. It is clear therefore that the new definitions have to be validated for reliability and diagnostic performance before they could be used both for research purposes and in clinical practice.

In this exercise, we decided to assess the agreement not only between radiologists but also between rheumatologists, including a young fellow with brief experience in imaging, in order to simulate the real-life scenario where radiographs are often read directly by clinician. The kappa values between the radiologists demonstrated that in expert hands the reliability of the definitions is always high (above 0.70) in the sites examined. The intra-reader reliability of the two radiologists is also substantial or perfect, meaning that both radiologists applied the definitions easily and that both of them perceived them in a similar way. On the other hand, inter-reader agreement between rheumatologists was lower (from 0.46 to 0.88 depending on the site) meaning that perception of the definitions was different by the two investigators, but they were coherently applied by each one of them as intra-reader agreement was substantial or optimal in all sites.

The highest kappa differences between radiologists and rheumatologists were in the medial meniscus and HC. Considering that most of the patients included in the study were affected by knee OA in advanced stage, the anatomical changes at the medial compartment characterised by joint rim reduction, osteophytes, cartilage thinning and meniscal protrusion, could make difficult the exact localisation of the deposition and explain the difference between the readers, with the rheumatologists probably less used in identification of changes in advanced OA (Figure 3). Further, the different skills between the young and the expert rheumatologist could be also

a reason of discordance between the rheumatologists. Reliability was good to substantial in all other sites, including tendons, capsule and synovial membrane probably thanks to the easiest localisation of these structures in radiography even in advanced grades of OA.

Regarding the criterion validity of radiography, it demonstrated an overall accuracy of 73% with a PPV of 88%, NPV of 66%, sensitivity of 54% and specificity of 92%. The highest specificity was found at the medial meniscus (100%) while the highest sensitivity was at the level of HC (48%). A reason for the low sensitivity could be the advanced OA of our patients that makes the identification and exact localisation of the deposits challenging. This study is the first to use ad hoc created definitions by a panel of experts for CPPD identification, and confirms the results of previous studies regarding specificity, but yielded a lower sensitivity than previous studies that tested radiography against SFA (pooled sensitivity of 59%) (27), and against histology (sensitivity of 75%) (9). Considering that one of the readers rated the images in both studies that adopting histology as the reference standard (LMS) (9), it is reasonable to conclude that the application of the new definitions seems to be stricter regarding the identification of CPPD than the “experienced based” identification, but this did not affect the specificity of the exam that was already at the highest levels.

Globally, the menisci proved to be the most reliable site independently of the experience of the reader, and overall offer the highest specificity for diagnosis. The HC resulted to be challenging to score for rheumatologists with a lower specificity than menisci and only slightly higher sensitivity. Further considering that HC positivity alone is only present in less than 20% of radiographs, and in none of the histological specimens whereas at least one meniscus was positive in all patients, HC could be considered as a “second choice” site to score in case of doubts at the menisci.

This study, that for the first time attempts a validation of radiography for identification of CPPD both in terms of reliability and criterion validity, has several strengths. The definitions used have been produced by a group of experts including members of the ACR/EULAR CPPD Classification Criteria working group and external musculoskeletal radiologists with expertise in CPPD, with the intent to allow a uniform diagnosis of patients with CPPD at radiography, so that it could be included in the classification criteria (21). The definitions have been tested both from radiologists and rheumatologists yielding good or substantial agreement while criterion validity confirmed the high specificity of the definitions for CPPD identification.

This study presents however some limitations. Patients with initial or no OA, that generally were less challenging to score, were very few (1 with Kellgren-Lawrence grade 1 and 8 with Kellgren-Lawrence grade 2), but probably by adding more patients with mild OA, would increase the diagnostic accuracy of radiography. Further, synovial membrane and tendons were not retrieved during surgery so diagnostic accuracy at those sites could not be calculated. Moreover, samples were not assessed for the presence of BCP crystals as optical microscopy is not sensitive enough for their identification even when alizarin red staining is used (30). However, identification of BCP crystals would not affect the results as the aim was to assess the diagnostic accuracy of radiography for CPPD. So, even in case of false positives radiography it would make no difference for the assessment of the accuracy if the calcifications were due to BCP. Another limitation was the lack of a standardization of radiographic protocols between different institutions of this multi-center study, and moreover another source of variability was the use of different imaging workstations for radiographs interpretation between radiologists and rheumatologists. While these may lead to some variation, they are both strengths and limitations of the study. The variations in technical parameters and in imaging workstations contribute to the generalizability of the results, and applicability of the study in rheumatology

practice. Finally, some DICOM files were of low quality creating some difficulties in the correct identification and location of deposits.

In conclusion, does radiography have a place in 2022 for CPPD detection? The answer is "definitely"! By using the new definitions, radiography demonstrated to be a reliable diagnostic test and offers an overall high specificity, that translated in patients' perspective means a high positive predictive value. The exact position of radiography in the diagnostic algorithm in clinical practice as well as its use for research purposes is still to be defined but for the first time "the king is naked" and an evidenced based approach on the utility of radiography in CPPD can be adopted.

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Figures Legend:

Figure 1*: A: histological sample of a meniscus with superficial CPP deposits. B: microscopic analysis of a meniscus sample on polarized light microscopy, confirming the presence of CPP crystals with the typical parallelepiped shape, with weak positive birefringence.*

Figure 2: *This flow chart shows the relationship between radiography and tissue analysis (reference standard)*

Figure 3*: radiographic image with divergent evaluation between readers. There was a disagreement between readers on the exact location of CPP deposition especially in the medial compartment. This could be due to the advanced grade of OA, that determines reduction of the joint rim and dislocation of the meniscus, generating overlapping of the anatomical structures in the X-ray.*

Tables:

Table 1*: imaging item definitions for radiography in CPPD. Modified from Tedeschi SK et al.* (21)

Definition of imaging items indicating calcification

ITEM	DEFINITION
Calcification on conventional radiograph in fibro- or hyaline cartilage	Linear or punctate opacities in the region of fibro- or hyaline articular cartilage that are distinct from denser, nummular radio-opaque deposits due to BCP deposition.
Calcification on conventional radiograph of synovial membrane or joint capsule	Linear or punctate opacities in the region of synovial membrane or joint capsule that are distinct from denser, nummular radio-opaque deposits due to BCP deposition.
Calcification on conventional radiograph of tendon	Linear or punctate opacities within tendons or entheses that are distinct from denser, nummular radio-opaque deposits due to BCP deposition.

***Table 2**: Kappa values for intra- and inter-reader agreement. Values from 0.01–0.20 are considered as none to slight agreement, 0.21–0.40 as fair, 0.41– 0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement.*

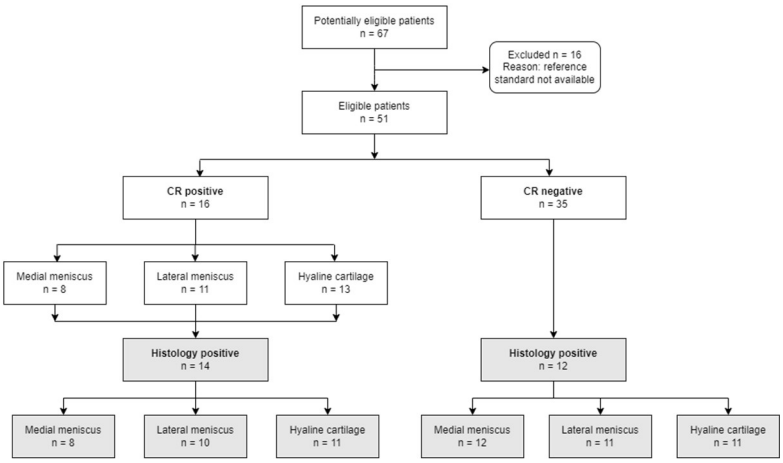
	Medial meniscus	Lateral meniscus	Hyaline cartilage	Quadriceps tendon	Patellar tendon	Joint Capsule	Synovial membrane	Menisci + cartilage	Entire joint
Inter-reader radio+rheuma	0.70	0.79	0.59	0.80	0.90	0.74	0.76	0.61	0.53
Inter-reader radio	0.82	0.76	0.70	0.91	0.88	0.82	0.79	0.61	0.49
Inter-reader rheuma	0.52	0.79	0.46	0.64	0.88	0.64	0.79	0.52	0.43
Intra-reader 1st radiologist	0.88	0.91	0.88	0.94	0.97	0.85	0.85	0.76	0.73
Intra-reader 2nd radiologist	1	0.91	0.97	1	1	0.97	1	0.97	0.94
Intra-reader expert rheumatologist	0.94	0.88	0.79	0.85	1	0.85	0.70	0.70	0.67
Intra-reader trainee rheumatologist	0.97	0.91	0.94	0.94	0.94	0.91	0.94	0.97	0.91

***Table 3**: 2 x 2 table shows the relationship between radiography and tissue analysis (reference standard)*

	Histology +	**Histology -**	Total
Radiography +	14	2	16
Radiography -	12	23	35
Total	26	25	51

***Table 4**: Sensitivity, specificity, PPV, NPV, accuracy of radiography for identification of CPPD by using the definitions developed by an international working group (members of ACR/EULAR CPPD classification criteria working group and external musculoskeletal radiologists). In parentheses 95% confidence intervals.*

	Medial meniscus	**Lateral meniscus**	**Hyaline cartilage**	**Overall**
Sensitivity	32% (15%-54%)	40% (21%-61%)	48% (27%-69%)	54% (33%-73%)
Specificity	100% (87%-100%)	96% (80%-100%)	93% (76%-99%)	92% (74%-99%)
Positive predictive value	100%	91% (58%-99%)	85% (58%-96%)	88% (64%-97%)
Negative predictive value	60% (54%-67%)	63% (55%-70%)	68% (59%-76%)	66% (55%-75%)
Accuracy	67% (52%-79%)	69% (54%-81%)	73% (58%-84%)	73% (58%-84%)



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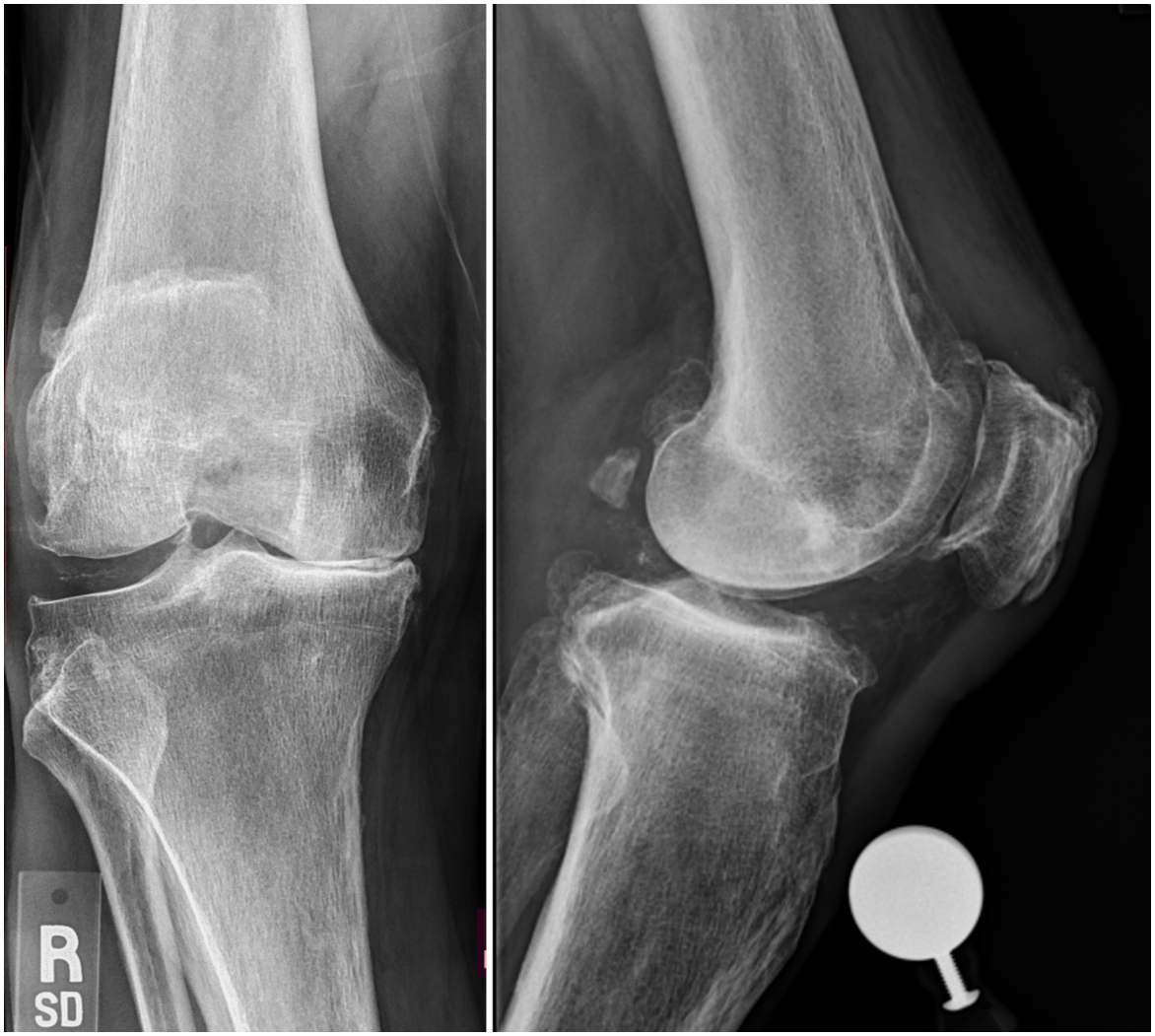

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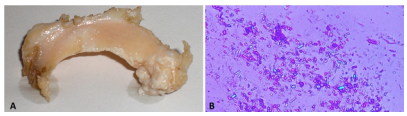

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