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ADVANCES IN IMAGING FOR THE ASSESSMENT OF CALCIUM PYROPHOSPHATE DEPOSITION DISEASE

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ABSTRACT – Calcium pyrophosphate (CPP) deposition (CPPD) disease is a common form of inflammatory arthritis. Despite its prevalence, it's an under-studied condition and its diagnosis is still challenging. Even if the gold standard for the identification of CPP crystals is still synovial fluid analysis, several different imaging modalities were evaluated and were increasingly used to avoid invasive procedures. Conventional radiography is still considered the first-line radiological investigation thanks to its widespread availability and the long tradition in CPPD disease. However, in the last years major imaging advances have occurred with ultrasound (US) and dual-energy computed tomography (DECT): US has travelled the furthest and is the only validated imaging technique in CPPD; while DECT is the most promising tool for CPPD identification thanks to its capability to discriminate CPP crystals from other calcific deposits. CT is frequently used in case of axial involvement of the disease, and the role of magnetic resonance imaging (MRI) in CPPD has only been marginally studied. All these imaging techniques could support progress in CPPD diagnosis and management, as well as provide a deeper insight into the pathogenesis, clinical manifestation, and the natural history of the disease. The purpose of this review is to highlight the current knowledge and the recent advances on the most used imaging modalities, and their promising value in diagnosing CPPD.

KEYWORDS: CPPD, Chondrocalcinosis, Ultrasound, X-ray, CT, DECT, MRI.

INTRODUCTION

Calcium pyrophosphate (CPP) deposition (CPPD) disease, according to the 2011 European Alliance of Associations for Rheumatology (EULAR) definition, is the umbrella term used to describe all the instances of deposition of CPP crystals in articular and periarticular tissues[1]. Based on the detection of radiographic chondrocalcinosis, CPPD has been estimated to affect 8-10 million people in the United States[2,3], but its actual prevalence is considered to be underestimated. The diagnosis of CPPD is traditionally based on Ryan and McCarty criteria[4]. According to them a "definite" diagnosis requires both the presence of microscopic identification of CPP crystals on synovial fluid analysis and the evidence of typical calcifications on radiography. If only one of these criteria is found, just a "probable" diagnosis can be made. In 2011 the EULAR recommendations supported synovial fluid detection of CPP crystals by polarized light microscopy as the gold standard for CPPD diagnosis, stating that a "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"[1]; confining imaging techniques to a minor role. However, even if synovial fluid analysis is still considered the gold standard in CPPD diagnosis, some limitations should be taken under consideration. Indeed, its sensi-

tivity is 70%, quite low for a screening test, that is due to the variability in microscopic characteristics of CPP crystals, their relative sparseness and small dimensions, and the well demonstrated operator dependence[5-7]. Moreover, it is not always possible to perform synovial fluid analysis, depending either on patients' characteristics or for technical issues.

In this setting, different imaging modalities have gained a growing interest in CPPD identification, because they could provide a harmless approach to CPPD diagnosis and monitoring, and they could contribute to understanding the pathogenesis and natural history of the disease as well as to better define the clinical features of CPPD.

The purpose of this review is to highlight the current knowledge and the recent advances on the most used imaging modalities in rheumatology clinical practice, mainly Ultrasound (US) and Conventional Radiography (CR) and their role in the assessment of CPPD.

CONVENTIONAL RADIOGRAPHY

Imaging evidence of CPPD has traditionally relied upon radiography, that is often considered the first-line radiological investigation in rheumatological clinical practice, given its low cost and widespread availability. Radiography can also offer a panoramic view of the entire joint for the evaluation of differential diagnosis or concomitant diseases, especially joint damage and degenerative changes[8,9]. Its main advantages are that the acquisition technique is standardized, and the training of the personnel as well as the interpretation of findings are quite simple, in comparison to other advanced imaging techniques.

Until the recent past, radiographic findings in CPPD were based on the concept of chondrocalcinosis, defined as the presence of calcification in joint cartilage. This entity was first identified in early 1960 by Zitnan and Sitaj[10], that have coined the term "chondrocalcinosis articularis". Chondrocalcinosis is most frequently found in knees, followed by wrists, hips, symphysis pubis and metacarpophalangeal joints[11,12]. Indeed, this sign is not specific to CPPD and other types of calcium crystals, in particular basic calcium crystals (BCP) may result in chondrocalcinosis. As suggested by the 2011 EULAR recommendations, even if radiographic chondrocalcinosis supports the diagnosis of CPPD, its absence does not exclude it[1], and moreover, in the light of the lack of specificity of this finding, we can definitely say that also its presence does not confirm the diagnosis. To overcome this problem, in 2021 a taskforce composed by an international group, including members of the American College of Rheumatology (ACR)/EULAR CPPD Classification Criteria working group and external musculoskeletal radiologists, acknowledged the need to standardise the diagnostic approach for CPPD and developed specific definitions for identification of CPPD on radiography. They attempted to revise the term "radiographic chondrocalcinosis", differentiating CPP deposits from other types of calcium crystals, in order to increase specificity to CPPD. According to these novel definitions CPP deposits on radiography are defined as "linear or punctate opacities in the region of fibro- or hyaline articular cartilage/synovial membrane or joint capsule/within tendons or entheses" (Figure 1), conversely BCP crystals appear as "denser, nummular radio-opaque deposits" and are typically periarticular in their locations[13].

Besides chondrocalcinosis, a series of other radiographic findings have been described in CPPD. The distribution of radiographic osteoarthritis (OA) in CPPD is frequently found in the 2nd and 3rd metacarpophalangeal joints, radiocarpal or glenohumeral joints, and is often associated with severe joint destruction. Additionally, other radiographic characteristics related with CPPD comprise large subchondral cysts, prominent osteophytes and tendon calcifications. These findings are quite atypical in comparison to OA without CPPD and may help in discriminating between subjects with CPPD and mimickers[14].

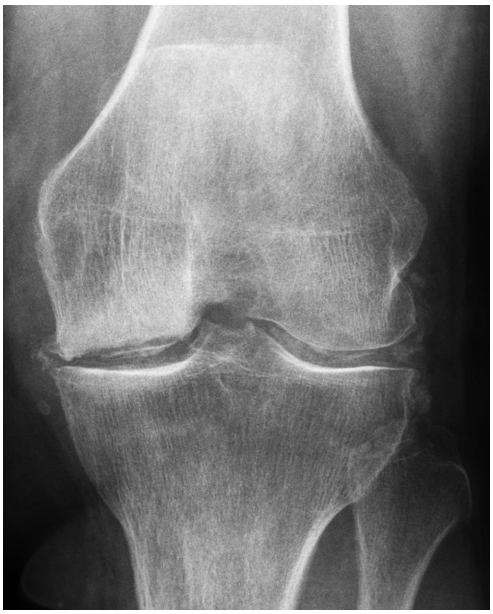

Figure 1. Calcium pyrophosphate deposits in conventional radiography: linear or punctate opacities in the region of fibro and hyaline cartilage.

Regarding the diagnostic performance of radiography in CPPD, its specificity is generally high, while its sensitivity is only moderate, though there is wide variability across studies, both for the lack of validated radiographic definitions until now and for the different gold standards adopted for CPPD confirmation. In a recent systematic literature review, radiography showed a pooled specificity of 96% (95% in comparison to synovial fluid analysis/histology as reference standard, and 95% compared to Ryan and McCarty criteria), but only moderate sensitivity (47% and 80% using as the reference methods synovial fluid analysis/histology or Ryan and McCarty criteria, respectively, with a pooled sensitivity of 60%)[15]. This can be due in part to the two-dimensional properties of radiography, and in part to the concurrence of osteoarthritis in CPPD, in which degenerative joint changes and the overlap of different anatomical structures, could influence the diagnostic accuracy of radiography.

Recently, the Outcome Measures in Rheumatology (OMERACT) US in CPPD working group explored the diagnostic performance of radiography in CPPD in comparison to US and histology as the reference standard at knee level, using the novel radiographic definitions[16]. This study confirms the high specificity of radiography in menisci, hyaline cartilage and in the overall evaluation of the knee (range from 93% to 100%), but it also supports its low sensitivity, with values ranging from 32% to 48% and an overall sensitivity of 54%. A reason for the low sensitivity may be the advanced grade of OA in the cohort of patients, degenerative changes with dislocation of menisci, thinning of hyaline cartilage and the overlap with other anatomical structures can make the exact localisation of deposits challenging. Further they also assessed the reliability of these definitions among musculoskeletal radiologists and rheumatologists with different grades of experience. The intra-reader agreement of the radiologists and the rheumatologist was from moderate to almost perfect in all knee structures (kappa range from 0.70 to 1), meaning that the novel definitions were easily applied by each one of them. Instead, while the inter-reader reliability among radiologists was always high (above 0.7), the inter-reader agreement among rheumatologists was lower (from 0.46 to 0.88), suggesting that the perception of the definitions was influenced by the experience of the reader[16].

ULTRASOUND

Over the last decades, musculoskeletal US has progressively gained a key role in rheumatological clinical practice and has changed the diagnostic approach for many rheumatic diseases. US, compared to other imaging techniques, is safe, less expensive, easily available, and not so much time-consuming. It can integrate information to clinical data, leading to an accurate diagnosis and an adequate decision-making process. US is a very sensitive exam and can achieve early identification of anatomical changes associated with early arthritis or persistent inflammatory process. Furthermore, it may be used for guidance in invasive procedures, making them safe and effective[17]. In addition, a major advantage of US is that can be directly performed during clinical evaluation, making it the preferred imaging modality for many rheumatologists. However, even if the list of advantages is quite long, it is still considered the most operator-dependent technique, because it requires adequate standardization of acquisition techniques as well as of imaging interpretation, and needs good operator training, that is quite long in comparison to other imaging modalities. Fortunately, all these apparent limitations can be overcome.

US in CPPD was described for the first time in 1990 by Kellner et al[18], who compared US to radiography, and concluded that US is a sensitive exam in revealing CPP calcification and can be considered for CPPD diagnosis, even if US findings cannot be considered pathognomonic. Indeed, in 1995, Coari et al[19] described the typical appearance of CPP deposits on US as "hyperechoic, linear images within the cartilage, parallel to bone surface". Moreover in 2006, when advances in US machines allowed for higher image resolution, Grassi et al[20], evaluated distinctive US features of CPP crystals in hyaline cartilage, fibrocartilage, and tendons, which can be distinguished from other crystal arthropathies by their conformation and anatomical location. And in 2007, Filippou et al[21] revealed the high specificity and sensitivity of US for CPPD diagnosis.

Thanks to this evidence, in 2011, EULAR experts published the recommendations for CPPD diagnosis recognizing the US as a useful promising technique for CPP crystals identification, with excellent sensitivity and specificity and even better than those of conventional radiography[1]. Otherwise, they underlined the need to fill some gaps in the validation process of US in CPPD, because so far, few studies from just a few centers had been published.

Since then, a growing number of studies have been published promoting the diagnostic value of US in CPPD. In 2016, a meta-analysis by Filippou et al[22] on the diagnostic performance of US showed a

pooled sensitivity of 87% and a pooled specificity of 98% when the reference standard was synovial fluid analysis. In comparison to radiography, US demonstrated a sensitivity of 58% and a specificity of 84%. While considering McCarty's criteria as reference test, US sensitivity was 34% and specificity was 100%. Finally, when the reference method was histology, US showed a sensitivity of 84% and a specificity of 93%, respectively. Taking into account the single anatomical structures, the highest value of sensitivity and specificity was found in hyaline cartilage (sensitivity of 77% specificity of 96%) and fibrocartilage (sensitivity of 77% and specificity of 97%), whereas tendons demonstrated weaker results.

Another study, in 2016, assessed the diagnostic accuracy of US in CPPD compared to synovial fluid analysis and radiography, considering histology as the gold standard[23]. The authors demonstrated that US was the most sensitive exam in CPPD diagnosis and synovial fluid the most specific. US showed a sensitivity of 96% and a specificity of 87%, as for synovial fluid were 77% and 100% respectively, and 75% and 93% for radiography.

A recent systematic literature review and metanalysis by Cipolletta et al[15] examined and compared the diagnostic accuracy of radiography and US in CPPD (**Table 1**). They included 26 studies evaluating the diagnostic performance of US and CR in comparison to synovial fluid analysis or histology. At knee level, considering synovial fluid analysis as the reference test, US showed an excellent sensitivity and specificity (85% and 91%, respectively). Similar results of sensitivity were confirmed using histology as the reference standard (sensitivity 93%); on the other hand, specificity value was lower (specificity 68%), this could be explained by the rigorous gold standard of histology. Besides, subjects enrolled in studies that considered histology as reference test underwent prosthetic surgery, so we can assume that they had higher grade osteoarthritis. However, one of the main problems is the great heterogenicity between studies, both for the US definitions used, for the joints assessed and for the reference standard adopted.

Table 1. Diagnostic accuracy of radiography and US in CPPD diagnosis.

	Sensitivity	Specificity	Diagnostic accuracy
Radiography	60%	96%	89%
Ultrasound	81%	90%	95%

To fill this gap, the OMERACT CPPD Ultrasound Subtask Force, following a stepwise approach, developed and validated a new set of ultrasonographic definitions for CPPD, based on expert opinion[24]. OMERACT defines CPP deposits by shape, echogenicity, localization and behavior in dynamic assessment as hyperechoic structures (similar to bone cortex) that do not create acoustic shadowing, of variable size and shape, localized within the fibrocartilage/hyaline cartilage/tendon, that remain fixed and move together with the cartilage/tendon during dynamic scanning (**Figure 2**). The definitions showed a good inter- and intra-reader reliability in static images and on patients at the level of knee hyaline cartilage, menisci and triangular fibrocartilage complex of the wrist, that are considered the most involved sites in CPPD[24,25]. Subsequently, the definitions have been validated at knee level (menisci and hyaline cartilage), using histology as the reference standard, and demonstrated to be accurate for CPPD diagnosis (accuracy of 75%), with an overall sensitivity of 91% and a specificity of 59%[26]. The group is now working on the development of an ultrasonographic scoring system for the quantification of CPP deposition. Knees, with menisci and hyaline cartilage, and wrists with triangular fibrocartilage complex (TFCC), were included in the final score, using a four-grade scoring system: grade 0: no images consistent with CPPD; grade 1: ≤3 single spots or 1 small deposit; grade 2: > 3 single spots or >1 small deposit or ≥1 larger deposit occupying ≤ 50% of the structure under examination; grade 3: deposits that occupy more than 50% of the structure under examination. In static images the inter- and the intra-reader reliability ranged from substantial to almost perfect in all the sites and in the overall evaluation (kappa range 0.61 - 0.86 and 0.73 – 0.89 respectively). On live scanning, the overall inter- and intra-reader reliability of the scoring was substantial (kappa 0.66 and 0.72 respectively), with HC of the knee demonstrated to be the most reliable site (kappa 0.77 and 0.87), while the TFCC showed the lowest kappa values (0.34 and 0.35 for inter- and intra-reader reliability)[27].

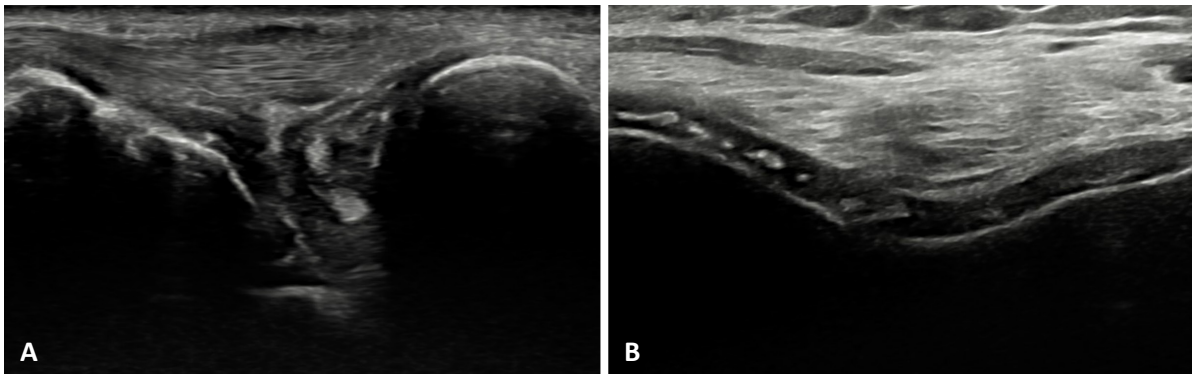

Figure 2. Calcium pyrophosphate deposits on ultrasound: hyperechoic structures (similar to bone cortex) that do not create acoustic shadowing, of variable size and shape, localized within the triangular fibrocartilage complex of the wrist (A) and hyaline cartilage of the knee (B).

OTHER IMAGING TECHNIQUES

Besides radiography and US, that are the most used imaging techniques in CPPD, in the last years a series of advanced imaging methods have demonstrated significant development in this field and have proven promising tools for CPP crystal identification.

Computed tomography (CT) is very useful in particular for the assessment of deep anatomical structures, for example in case of axial involvement as crowned dens syndrome, and for the mapping of CPP deposits[28]. It can discriminate different types of calcium crystals only by morphology and location, but it does not permit the molecular characterization, in particular between CPP and BCP deposits. An international group of rheumatologists and radiologists defines CPP deposits as "well-defined, linear or punctate, less dense than cortical bone, located within cartilage/synovial membrane/joint capsule/tendons", that are distinct from BCP deposits, that are "larger, homogeneous and well-defined ("cloudlike"), and denser in the formative and resting phases, but become fluffy, ill-defined, and less dense during episodes of crystal resorption"[13].

In comparison to conventional CT, more advanced modalities can provide information on the molecular composition of tissues, such as the dual-energy CT (DECT), which characterize different tissues by utilizing simultaneously two different X-ray beams (of 80 and 140 kV)[29]. Thanks to this capability, DECT has been increasingly used to discriminate monosodium urate (MSU) crystals from other types of deposits in gout and was applied in CPPD only recently. It was used for the first time in phantom model, demonstrating its capability to differentiate CPP crystals suspensions from those with MSU[30]. A proof-of-concept study on 40 patients showed that CPP deposits in menisci can be differentiated from calcification-free menisci and from BCP calcifications, thanks to specific DECT parameters (dual-energy index (DEI) between 0.016-0.036)[31]. Recent data demonstrated an excellent sensitivity (from 78% to 100%) and specificity (94%) of DECT in CPPD diagnosis[32,33]. However, it is still unclear how DECT can improve the sensitivity for CPPD detection provided by CT, also in CT-invisible chondrocalcinosis[34].

The role of magnetic resonance imaging (MRI) in CPPD diagnosis has been only marginally evaluated, and the few studies provided conflicting results. Even if it can offer great anatomical details, calcific structures, such as CPP deposits, are poorly visualized as negative images within joint structures, and it non capable to characterize the types of calcium deposits. Two *in vivo* studies demonstrated that MRI was more sensitive in comparison to radiography in detecting CPP crystal calcifications, in particular with T1-weighted gradient-echo sequences[35,36]. On the other hand, one *ex vivo* study showed a low sensitivity of MRI in CPPD diagnosis[37].

All these imaging techniques are not used routinely in clinical practice, and it is still unclear their added value, given that radiographic or ultrasonographic characteristics of CPP deposits are quite simple to identify, and that radiography and US are more feasible and accessible in clinical practice.

CONCLUSIONS

In the last decades, advances in imaging technology have significantly changed the approach to patients in rheumatological clinical practice and have considerably contributed to understanding the pathogenesis and the natural history of many rheumatological disorders. Nonetheless, some of the main unmet

needs regarding the use of imaging in CPPD concern the scarcity of standardized and universally accepted definitions for CPPD calcification detection[387], and the absence of validated scoring systems to follow the patient over time. To fulfil these important issues, that preclude the use of imaging in clinical trials, the OMERACT US in CPPD working group recently defined and validated the ultrasonographic characteristics of CPPD in articular and periarticular tissues. In parallel an international working group composed by members of the ACR/EULAR CPPD Classification Criteria taskforce and external musculoskeletal radiologists, developed a set of expert-based imaging item definitions for radiography, CT, DECT and MRI[13].

Imaging techniques to be considered as outcome measures should be validated and should demonstrate adequate diagnostic accuracy. Conventional radiography has historically been considered the cornerstone for CPPD diagnosis by imaging and demonstrated to be a very specific exam for CPPD identification, even if it presents a sub-optimal sensitivity. On the other hand, US has travelled the furthest among imaging modalities: it is the most validated technique and resulted more accurate than radiography in CPP crystal detection. DECT is a promising tool capable of characterizing CPPD from other calcium deposits, but it is expensive and not widely available in clinical practice. CT is frequently used in case of axial involvement, but its diagnostic accuracy is not adequately evaluated, and the role of MRI in CPPD has only been slightly studied with conflicting results.

The last decades have seen enormous advantages in imaging technology, but the path to the summit is still long. The future research agenda should include the validation of the novel definitions of radiography, CT, DECT and MRI, and the development of a feasible imaging scoring system to assess the extent of CPP deposits at patient level, to ensure an adequate patient follow-up, and to provide a deeper insight into natural history of CPPD.

Conflict of interests:
The authors declare that they have no conflict of interest to disclose.

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