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Editorial

Diagnosis of calcium pyrophosphate deposition by imaging – current state and challenges remaining

As per the European League Against Rheumatism (EULAR) recommendations, calcium pyrophosphate (CPP) deposition (CPPD) is the umbrella term for all instances of CPP crystal occurrence[1]. Unlike ectopic calcifications of basic calcium phosphate (BCP) which are ubiquitous, CPP deposits occur almost exclusively in articular tissues, most commonly fibrocartilage and hyaline cartilage, and typically in the knee[2]. While CPPD is the most common cause of chondrocalcinosis, other types of calcium crystals may be involved[1,3].

Although CPP-related arthritis is the third most common inflammatory arthritis and CPPD prevalence is increasing due to the aging population - affecting 0.42–0.52% of the general population and ~8–10 million people in the United States of America when estimated by detection of radiographic chondrocalcinosis[3,4] - this disease has attracted far less attention in the literature than other common types of arthritis such as gout and rheumatoid arthritis. Besides the fact that CPPD may be asymptomatic and therefore underdiagnosed, and that treatment options remain limited as no drug is currently available to prevent calcium crystal deposition nor permit its dissolution[1,2], the lack of an accurate and reliable imaging technique capable of non-invasively detecting, characterizing, quantifying, and mapping CPP deposits *in vivo* certainly contributes to this problem.

To date, the definitive diagnosis of CPPD remains by identification of typical CPP crystals (rhomboid-shaped, positively birefringent) in synovial fluid (or occasionally biopsied tissue), usually by compensated polarized light microscopy, as first suggested by McCarty *et al.*, in 1962[5] and recommended by EULAR in 2011[1]. However, limitations of synovial fluid analysis have been recognized, especially due to the variability in morphology and birefringence characteristics of CPP crystals, as well as their relative sparseness and varying localization in and around joints[4]. Among widely available regular imaging techniques, conventional radiography should be part of the initial assessment, even though its sensitivity is low (as low as 29% in certain circumstances) for detecting chondrocalcinosis[1,3]. While not being the ideal screening tool, X-rays still provide an overview of the affected joint and are used to search for other radiographic features of the disease and its differential diagnosis[3]. Furthermore, it is worth mentioning that while radiographic chondrocalcinosis may be a useful imaging marker and supports the diagnosis of CPPD, its absence does not exclude it[1]. Conversely, other types of calcium crystal deposits such as BCP may result in chondrocalcinosis[3], thereby highlighting the lack of specificity of this sign. Computed tomography (CT) is more accurate and reliable than conventional radiography, particularly for the evaluation of deep anatomical structures in cases of axial skeletal involvement of CPPD. Despite its advantages such as quantification and mapping of calcium crystal deposits, CT is rarely used for assessing peripheral joints[6]. However, it should be noted that conventional CT does not enable the distinction between CPP and BCP crystal deposits unlike more advanced emerging imaging techniques such as dual-energy CT (DECT)[7] and multi-energy photon-counting CT[8,9]. To date, the potential role of magnetic resonance imaging (MRI) in CPPD has only been marginally investigated[10,11]. In contrast, ultrasound (US) has generated much more interest and been increasingly used for the diagnosis of CPPD over the past decade. Ultrasound has proven useful in identifying calcifications in peripheral joints, particularly the knee, yielding higher pooled sensitivity (34–77%) and specificity (92–100%) than conventional radiography when considering each joint structure and variable reference standards[12]. However, this recent systematic literature review with meta-analysis also emphasized that although the diagnostic accuracy of US in CPPD was relatively high in all studies, the definitions used for US characteristics of CPPD varied considerably[12]. This prompted the formation of the outcome measures in rheumatology (OMERACT) US CPPD task force with the aim of first agreeing on the US features and definitions of CPP deposits in joints and periarticular tissues, and then assessing their reliability[13].

In this Issue of the Journal, Lee *et al.* aimed to assess the diagnostic performance of US for CPPD in meniscal fibrocartilage, hyaline cartilage, quadriceps and patellar tendons, and synovial fluid of the knee, further evaluating its inter- and intraobserver reliability. They studied a total of 174 patients (43 with CPPD and 131 controls, of which 67 with knee osteoarthritis) who underwent both conventional radiography and US of the knee, using compensated polarized light microscopic analysis of synovial fluid aspiration as reference standard for the diagnosis of CPPD. Applying the recently established OMERACT definitions for US features of CPPD in joints and periarticular tissues[13], the authors found that US had a sensitivity and specificity of 74.4% and 77.1%, compared with 44.2% and 96.9% for conventional radiography, respectively. They also reported excellent inter- and intraobserver reliability with US ($\kappa \geq 0.817$), except for tendons ($\kappa = 0.532–0.788$). In addition, Lee *et al.* concluded that the combined US assessment of menisci, hyaline cartilage, and tendons yielded the best diagnostic accuracy for CPPD in the knee.

While the authors are to be commended for having accomplished such an exciting piece of work sparking new insights into the diagnostic role of US in CPPD of the knee, the study by Lee *et al.* also raises a few comments and concerns. First, a major issue is, as with previous US studies[12,13], the concern for exposure misclassification since the reference standard used was synovial fluid analysis. As previously mentioned, compensated polarized light microscopy of synovial fluid can be challenging and is not the ideal 100%-accurate gold standard[4], especially when considering

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CPP crystal deposits in various joint structures. As a result, patients with CPPD may be misidentified as controls (i.e., false negatives), and vice versa. This might explain the slightly lower than expected diagnostic accuracy of US in this study. Secondly, it should be noted that OMERACT definitions for US features of CPPD are expert-opinion based[13], and the so-called "CPP" deposits identified by US could actually be a mixture of CPP and BCP crystals or composed solely of BCP. The latter is particularly likely to be true for synovial fluid and tendon calcifications. In fact, there are currently no definitions available for US features of BCP crystal deposition deep within joints (fibrocartilage, hyaline cartilage, and synovial fluid) and, to date, no study has conclusively proven that US detected lesions in tendons according to OMERACT definitions were indeed true pure CPP deposits. This might explain the lower agreement for tendon involvement, both here and in previous US studies[12,13], and the comparable prevalence of "CPP" deposits in the patellar tendon and synovial fluid between cases and controls in this study.

The future research agenda for the diagnosis of CPPD by imaging should include the following. First, US should be further validated using highly specific crystal analytic methods such as Raman and Fourier-transform infrared spectroscopy, which are currently being adapted for clinical use[11,14]. In addition, US would benefit from better definition and standardization of scanning protocols[12,13]. Then, based on promising initial results recently reported both in vitro[8,9] and ex vivo[7–9], the diagnostic performance of advanced imaging techniques such as DECT and multi-energy photon-counting CT should be thoroughly assessed *in vivo*. Furthermore, their potential for characterization, quantification, and mapping of calcium crystal deposits in both peripheral and axial skeletal CPPD should also be scrutinized. The upcoming greater availability of such systems, the latest technological advances and optimization of protocols (in terms of data acquisition, image reconstruction, and post-processing) should lead to their wider clinical use. On the other hand, initial experiments have also been undertaken to apply photon-counting detector technology in radiography. Spectral photon-counting radiography should thus be investigated in the same fashion as its 3D counterparts. Finally, the further development and clinical application of specific MRI pulse sequences, such as ultrashort echo time[10] and susceptibility-weighted imaging[15], is eagerly awaited. Such novel sequences should allow for the comprehensive assessment of affected joints with concomitant quantification of calcium crystal burden using MRI. In conclusion, all these emerging imaging techniques are expected to help advance the diagnosis and management of CPPD by enhancing its non-invasive identification *in vivo*, thereby providing a deeper insight into the impact of CPPD on joint pathology phenotypes.

Conflict of interest

None.

Acknowledgments

None.

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