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CRYSTAL ARTHRITIS (L STAMP, SECTION EDITOR)

Issues in CPPD Nomenclature and Classification

Sara K. Tedeschi[1]

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Abstract

Purpose of Review This paper covers confusion and challenges in the nomenclature of calcium pyrophosphate deposition disease. Clinicians, investigators, and patients are faced with a variety of terms that are used to describe CPPD and its phenotypes, and clarity is greatly needed to help advance research and patient care. Motivation for the upcoming development of CPPD classification criteria is reviewed.

Recent Findings EULAR proposed recommended terminology for CPPD in 2011. International Classification of Diseases (ICD-9 and ICD-10) billing codes identify definite or probable CPPD with variable accuracy depending on the clinical setting and comparator group. READ diagnostic codes have been employed to identify pseudogout in UK datasets but their accuracy has not been evaluated. CPPD classification criteria will provide a system for identifying a relatively homogenous group of patients to be included in clinical studies, enabling comparison of outcomes across studies.

Summary CPPD nomenclature remains challenging for clinicians, investigators, and patients. A lay-friendly definition of CPPD, using easily accessible terminology, would be welcome. CPPD classification criteria are a necessary step in moving forward CPPD clinical research and may involve a range of clinical, laboratory, and imaging modalities.

Keywords CPPD · Pseudogout · Acute CPP crystal arthritis · Classification criteria · Terminology · Nomenclature

Introduction

Calcium pyrophosphate deposition (CPPD) disease represents a crystalline arthritis that predominantly affects older adults. Our understanding of CPPD prevalence is driven by chondrocalcinosis, a radiographic finding estimated to exist in 10 million adults in the USA [1••]. As the population ages, CPPD prevalence is expected to increase and yet this disease remains under-studied since McCarty and colleagues reported their initial case series in 1962 [2, 3]. Clinicians often use the terms *chondrocalcinosis*, *CPPD*, and *pseudogout* interchangeably in clinical notes and to patients. This is akin to saying that *hyperuricemia* (a laboratory abnormality) and *gout* (arthritis in which hyperuricemia plays a pathogenic role) are one and the same, and yet most clinicians would clearly distinguish between hyperuricemia and gout. Numerous CPPD experts have noted that confusing nomenclature and a lack of classification criteria hinder our understanding of this common arthritis [1, 4, 5]. This review highlights updates in CPPD nomenclature and classification in the past decade, with a focus on the past five years.

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✉ Sara K. Tedeschi
stedeschi1@bwh.harvard.edu

[1] Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, 60 Fenwood Road, Boston, MA 02115, USA

Nomenclature and Its Implications

The first sentence of this review provides fodder for debate: is it "CPPD" (calcium pyrophosphate deposition) or "CPDD" (calcium pyrophosphate deposition disease, or calcium pyrophosphate dihydrate deposition)? A search of titles and abstracts from PubMed indexed articles in the past decade revealed that "CPPD" ($n = 207$) was much more common than "CPDD" ($n = 35$). Distinguishing between CPPD and CPDD may be splitting hairs, but numerous other terminology issues pose challenges to characterizing and studying this disease.

Labeling Disease Phenotypes

McCarty and colleagues "initially termed the syndrome associated with calcium pyrophosphate dihydrate (CPPD) deposition 'pseudogout' [in 1962] because of the obvious parallel

with true (urate) gout." [2, 6] They later suggested that *pseudogout* "be reserved for the acute episodes associated with CPPD crystals," as many patients with joint pain did not develop acute attacks [6].

In 1985, Ryan and McCarty proposed 5 phenotypes of *calcium pyrophosphate dihydrate* (*CPPD*) *crystal deposition disease* based on observations among > 450 cases (Table 1) [6]. They dubbed many of these phenotypes "pseudo" due to their mimicry of other arthritic conditions. One of their phenotypes, characterized by osteoarthritis with CPPD deposits, has yet another moniker in Europe: *pyrophosphate arthropathy* [7].

In 2011, the European League Against Rheumatism (EULAR) CPPD Task Force proposed new terminology for CPPD [5]. One of the goals was to address the variable usage of terms such as *pseudogout* and *chondrocalcinosis* to describe CPPD and is phenotypes. The EULAR Task Force recommendations were informed by a systematic literature review and expert consensus. The group recognized 4 phenotypes of *calcium pyrophosphate deposition* (CPPD) (Table 1). In a major departure from Ryan and McCarty's phenotypes, the Task Force eliminated the prefix "pseudo" from CPPD phenotypes because it does not specify the causative crystals, suggests that calcium pyrophosphate (CPP) crystals are less important than monosodium urate crystals, and causes confusion among patients. The Task Force also recommended using the term *cartilage calcification* in place of *chondrocalcinosis* and noted that it may be due to deposition of CPP crystals or other calcium crystals.

Labeling Disease Elements

The Gout, Hyperuricemia, and Crystal-Associated Disease Network (G-CAN) recently published a consensus statement regarding labels and definitions for disease elements in gout [8]. Similar to the EULAR CPPD Task Force methodology, the G-CAN Gout investigators began with a literature review and used a Delphi exercise to achieve expert consensus. The intention was to develop a lexicon of standardized terms for use in gout research and clinical care. For example, an episode of acute inflammation triggered by monosodium urate crystals should be called a *gout flare*, rather than gout attack or other possible descriptors.

A similar exercise would benefit CPPD research and clinical care given the imprecise usage of the terms CPPD, pseudogout, and chondrocalcinosis. An international effort to develop standardized language for CPPD, using simplified terms rather than mouthfuls of abbreviations, could bring clarity to this disease.

Making CPPD an Approachable Disease

A patient presenting for evaluation of joint pain expects to leave the visit with a diagnosis. He or she may wish to read more about the diagnosis, or to share the diagnosis with family or friends. A patient who is told that he/she has "CPPD" or "CPDD" or "pseudogout" may not be able to recall these names later or may misinterpret the latter as "gout."

EULAR and ACR recently developed a "common language" description of rheumatic and musculoskeletal diseases [9]. The intent was to succinctly describe these conditions as a whole using language that is understood by patients, the lay public, media, healthcare providers, policymakers, health insurance providers, charities, and employers. A lay-friendly definition of CPPD using approachable, simple language would be a breath of fresh air for patients, providers, and other stakeholders.

Diagnostic Criteria

Ryan and McCarty proposed diagnostic criteria for CPPD in 1985, which remain the only set of diagnostic criteria for this disease. The diagnostic criteria have a simple structure and do not delve into CPPD phenotypes:

"A case is considered 'definite' if CPPD crystals are demonstrated in tissues or synovial fluid by definitive means, such as by x-ray diffraction, or if crystals compatible with CPPD are demonstrated by compensated polarized light microscopy and typical calcifications are seen on roentgenograms. If only one of these criteria is found, a 'probable' diagnosis is made." [6]

In clinical practice, x-ray diffraction is not routinely performed to evaluate for the presence of CPPD crystals. Definite diagnosis therefore requires both the presence of synovial fluid CPP crystals and x-ray chondrocalcinosis. However, a patient with acute monoarthritis and synovial fluid aspirate with intracellular CPPD crystals might not undergo x-ray. Most if not all clinicians would consider this patient to have "definite" CPPD, although this patient only has "probable" CPPD per Ryan and McCarty's diagnostic criteria.

This single set of diagnostic criteria has not been validated in other CPPD populations, meaning that their sensitivity and specificity for CPPD remain unknown. The diagnostic criteria also do not specify whether joint pain or swelling is required for diagnosis. Ryan and McCarty's diagnostic criteria may be most helpful in focusing our attention to pathogenic role of CPP crystals in this disease. In the current era of advanced imaging modalities, the need for and type of radiographic evidence warrants reconsideration. In a patient with synovial fluid CPP crystals, radiographic evidence may not be required to make the diagnosis. A number of studies using synovial fluid CPP crystals as the reference standard suggest that x-ray sensitivity for CPPD is generally around 40%, meaning that a large percentage of CPPD patients might not meet the diagnostic criteria due to a negative x-ray [10–13]. A growing body of literature supports ultrasound accurately identifies CPPD, and emerging data suggest that dual-energy CT and

Table 1 Comparison of CPPD phenotypes and terminology

	Ryan and McCarty (1985)[1]	EULAR Task Force (2011)[2]
Overall disease entity	Calcium pyrophosphate dihydrate (CPPD) crystal deposition disease	Calcium pyrophosphate deposition (CPPD)
Asymptomatic phenotype	Asymptomatic (lanthanic) calcium pyrophosphate dihydrate crystal deposition: lack of joint symptoms in a joint with x-ray chondrocalcinosis.	Asymptomatic CPPD: isolated cartilage calcification or osteoarthritis with cartilage calcification of no apparent clinical consequence
Osteoarthritis phenotype	Pseudo-osteoarthritis: progressive degeneration of multiple joints—particularly the knee, wrist, metacarpophalangeal, hip, elbow, ankle, and shoulder joints—that is generally symmetric, with or without x-ray chondrocalcinosis, with or without episodic acute attacks of pseudogout.	Osteoarthritis with CPPD: CPP crystal deposition in a joint that also shows changes of osteoarthritis. (The EULAR Task Force noted that it remains unclear whether osteoarthritis with CPPD clinically differs from osteoarthritis without CPPD in terms of symptoms, joint distribution, and outcomes.)
Acute inflammatory arthritis phenotype	Pseudogout: acute or subacute arthritis attacks lasting 1 day to 4 weeks, self-limited, involving 1 or a few appendicular joints	Acute CPP crystal arthritis: acute onset, self-limited synovitis with CPP crystal deposition
Chronic inflammatory arthritis phenotype	Pseudorheumatoid arthritis: polyarticular involvement with joint inflammation "out of phase" (rather than simultaneous), subacute attacks lasting 4 weeks to several months, with osteophyte formation, lack of erosions, and intracellular CPPD crystals.	Chronic CPP crystal inflammatory arthritis: chronic inflammatory arthritis associated with CPP crystal deposition
Destructive arthropathy phenotype	Pseudoneuropathic joints: destructive arthropathy, with or without tertiary syphilis	
Rare phenotypes	Other rare phenotypes: spinal involvement with bony ankylosis, meningeal irritation or radiculopathy; and "tophaceous" mass of CPPD crystal deposits.	

[1] Ryan L, McCarty D. Calcium pyrophosphate crystal deposition disease; pseudogout; articular chondrocalcinosis. In: McCarty D, ed. Arthritis and allied conditions. 10th ed. Philadelphia: Lea & Febiger; 1985:1515–46

[2] Zhang W, Doherty M, Bardin T, et al. European league against rheumatism recommendations for calcium pyrophosphate deposition. Part i: Terminology and diagnosis. Ann Rheum Dis 2011;70:563–70

multi-energy spectral photon-counting CT may have excellent performance in CPPD as well [14–17].

Diagnosis Codes

When it comes to coding a clinical encounter for CPPD, the confusion continues. The International Classification of Diseases, 9th revision (ICD-9) provides > 12,000 diagnostic codes that serve as the basis for billing in the USA and other countries [18]. ICD-9 does not contain codes specifically labeled *CPPD* or *pseudogout*. McCarty and colleagues first described the "pseudogout syndrome" in 1962, meaning that this disease may have not been widely recognized when ICD-9 was being developed in the 1970s [2]. ICD-9 contains several codes for *chondrocalcinosis*, distinguished by the culpable crystal (Table 2). The ICD-9 diagnosis *other disorders of calcium metabolism* (275.49) can be used to code for CPPD. However, this code also represents calciphylaxis, nephrocalcinosis, vascular calcification, and apatite-related arthropathy among other conditions, meaning that it is not specific for CPPD [19]. Clinicians that are unsure of which ICD code to choose for CPPD or pseudogout might simply choose a code for *inflammatory arthritis*.

The 10th revision (ICD-10), developed in the 1990s and implemented in 2015 in the USA, unfortunately does not include codes specifically labeled *CPPD* or *pseudogout*. Like ICD-9, it includes codes for chondrocalcinosis and disorders of calcium metabolism (Table 2), with an additional code for the rare occurrence of familial chondrocalcinosis.

Identifying CPPD Using Diagnosis Codes

Bartels and colleagues recently developed the first-ever administrative claims-based algorithm for definite or probable CPPD using Veterans' Administration (VA) data from the Zablocki VA Medical Center [20••]. The algorithm was developed among patients with ICD-9 codes relevant to CPPD (712.1*, 712.2*, 712.3*, or 275.49), gout, or rheumatoid arthritis. Medical records were reviewed for the gold standard definition of definite or probable CPPD according to Ryan and McCarty's diagnostic criteria [6]. The final algorithm was the presence of ≥1 ICD-9 code (712.1*, 712.2*, 712.3*, or 275.49), which had sensitivity of 98% (95% CI 96–99%), specificity of 78% (74–83%), and positive predictive value (PPV) of 91% (88–94%) for definite or probable CPPD.

The authors then applied the algorithm to nationwide VA data and identified 25,157 patients classified as definite or probable CPPD [21]. Compared with age- and sex-matched general patients without ICD-9 codes for CPPD, those classified as definite/probable CPPD were more likely to have ICD-9 codes for hyperparathyroidism, gout, osteoarthritis, rheumatoid arthritis, hemochromatosis, and chronic kidney disease. Prescriptions for loop diuretics and proton pump inhibitors were less common among patients with CPPD vs. without CPPD.

We applied Bartels et al.'s CPPD algorithm at Partners HealthCare to evaluate its performance in an academic medical center electronic health record (EHR) [22]. Whereas Bartels et al. developed the algorithm among patients with ICD-9 codes for CPPD, gout, or rheumatoid arthritis, we tested the algorithm only among patients with ICD-9 codes for CPPD (Table 2). (Algorithm sensitivity was 100% in our sample, as all patients had ≥1 ICD-9 code for CPPD.) We reviewed 100 randomly selected medical records for definite or probable CPPD according to Ryan and McCarty's diagnostic criteria [6]. The published CPPD algorithm had a positive predictive value of 68% (95% CI 55–81%) for definite or probable CPPD. Among patients with ≥1

Table 2 Mapping of ICD-9 and ICD-10 diagnosis codes and labels pertinent to CPPD

ICD-9		ICD-10
275.49 Other disorders of calcium metabolism	→	E83.59 Other disorders of calcium metabolism
712.1* Chondrocalcinosis due to dicalcium phosphate crystals	→	M11.8* Other specified crystal arthropathies
712.2* Chondrocalcinosis due to pyrophosphate crystals	→	M11.8* Other specified crystal arthropathies
712.3* Chondrocalcinosis cause unspecified	→	M11.2* Other chondrocalcinosis
none		M11.1* Familial chondrocalcinosis

ICD-9 code for CPPD that did not fulfill Ryan and McCarty's diagnostic criteria, the most common clinical diagnosis was renal-related calcium disorder such as calciphylaxis (ICD 275.49). Other clinical scenarios included crowned dens syndrome (without fulfilling the diagnostic criteria), osteoarthritis without chondrocalcinosis on radiology reports, inflammatory arthritis, and crystal-proven gout.

In summary, ICD billing codes identify definite or probable CPPD with variable accuracy depending on the clinical setting and comparator group.

Identifying Pseudogout Using Diagnosis Codes

In the UK, diagnoses are indicated by READ codes rather than ICD codes. Several groups have employed READ codes recorded by general practitioners to identify pseudogout patients for nested case-control studies in the past decade [23, 24].

Rho et al. studied risk factors for pseudogout in a nested case-control study of 795 pseudogout cases and 7770 matched controls in The Health Improvement Network (THIN) dataset [23]. Pseudogout was defined as the presence of at least one READ code for pseudogout (N02.14) recorded by a general practitioner and the absence of a READ code for gout. Hyperparathyroidism, osteoarthritis, and loop diuretics were associated with increased risk for pseudogout, while thiazide diuretics were not associated with pseudogout risk.

Roddy et al. recently performed a nested case-control study focused on bisphosphonate use and pseudogout risk in the UK Clinical Practice Research Datalink (CPRD) [24]. Pseudogout was defined by on one READ code (N02.14) from a general practitioner. Among 2011 pseudogout cases matched to 8013 controls, pseudogout risk was higher among patients that were prescribed an oral bisphosphonate in the prior 60 days.

It bears mentioning that the accuracy of one READ code for pseudogout (N02.14) has not been validated against medical record review. A READ code for pseudogout might represent a broader diagnosis of CPPD, or acute CPP crystal arthritis (i.e., pseudogout), or a combination of these and other conditions. In prior validation work using CPRD data, READ codes, and medical record review, rheumatoid arthritis was overreported by general practitioners in the CPRD compared with rheumatologists [25]. Conversely, musculoskeletal diseases were underreported in the CPRD compared with other general practice databases. A single READ code recorded by a general practitioner therefore may or may not accurately represent pseudogout.

We are evaluating a novel machine learning approach for identifying pseudogout (acute CPP crystal arthritis) using EHR data. Given the lack of specific ICD codes for pseudogout, accurate identification of this phenotype requires rich information from narrative notes in the EHR combined with laboratory and radiology data. In preliminary work, adding information from a simple text search of narrative notes modestly improved the PPV for definite or probable pseudogout, defined as synovitis plus either synovial fluid CPP crystals or chondrocalcinosis (PPV 24% using ICD-9 codes alone vs. PPV 33% using ICD-9 codes plus simple text search) [22]. Our machine learning approach achieved a robust PPV of 81% for definite or probable pseudogout when applied to our academic medical center EHR dataset (manuscript in preparation).

In summary, READ codes have been employed to identify pseudogout but their accuracy has not been evaluated. Given the challenges with CPPD nomenclature and diagnosis, evaluating the accuracy of these codes would be a welcome contribution to the field. Incorporating information from narrative notes with billing codes improves the accuracy of identifying pseudogout in EHR data.

Classification Criteria for CPPD

CPPD has been widely recognized as a disease for over 60 years, although classification criteria for research studies have not been developed or validated. As a result, CPPD clinical research studies have often used Ryan and McCarty's (non-validated) diagnostic criteria or a variation thereof to define the study population. Fortunately, ACR and EULAR were recently awarded joint support for development of CPPD classification criteria that will facilitate research in this field.

Why Are Classification Criteria Needed?

Classification criteria are applied when selecting participants for clinical research studies to ensure a degree of homogeneity among the study population. Whereas diagnostic criteria aim to encompass every patient with the disease of interest (i.e., 100% sensitive for the disease), classification criteria aim to achieve 100% specificity while also achieving high sensitivity. The ideal classification system classifies all cases as cases and does not misclassify any controls as cases [26]. Patients classified with the disease consequently have similar characteristics; one or more characteristics may be mandatory for classifying a patient with the disease. Clinical studies that employ the same classification criteria include similar study populations, and their results can be more easily compared against one another.

As discussed above, CPPD is a heterogeneous disease with many phenotypes. A classification system will enable classification of patients with different phenotypes who all share some common features. To develop the classification system, investigators will employ a data-driven process complemented by expert consensus. The final set of classification criteria will likely assign weights to each criterion, as has been done for gout, rheumatoid arthritis, and systemic lupus erythematosus among other rheumatic diseases [27–29]. Criteria weights are summed for each patient; if the sum exceeds a threshold score, then the patient is classified as having the disease.

The presence of CPP crystals will likely carry substantial weight in the classification system and may be one of the more straightforward decisions. Other questions will not be as clear; for example, will the presence of CPP crystals alone (without joint pain) be sufficient for classifying a patient as having CPPD? Should patients with crowned dens syndrome, a rare manifestation of this disease, who lack other features of CPPD be classified? These and other decisions will be discussed and tested throughout multiple phases of criteria development.

Motivating an Interest in CPPD Research

Gout and CPPD each affect 8–10 million adults in the USA [1••, 30]. Despite their similar prevalence, gout research has garnered much more attention than CPPD. The number of CPPD publications indexed on PubMed (title/abstract containing "CPPD," "CPDD," "pseudogout," or "chondrocalcinosis") from 1996 to 2005 ($n = 398$) increased only slightly during the next decade, ($n = 470$ from 2006 to 2015). During these same decades, the number of gout publications more than doubled, reaching $n = 2685$ from 2006 to 2015 [31]. The EULAR 2011 CPPD Task Force Terminology and Diagnosis guidelines have been cited by 46 PubMed indexed manuscripts as of June 2019. The 2015 ACR/EULAR Gout Classification Criteria—published 4 years later—have already been cited by nearly the same number of manuscripts ($n = 43$).

Development of CPPD classification criteria will facilitate CPPD research, hopefully motivating an increase in the amount of research into this disease to ultimately improve our ability to prevent and treat it.

CPP Crystal Identification and Classification Criteria

Calcium pyrophosphate crystals are a common feature across all phenotypes and will likely play an important role in CPPD classification. However, the gold standard for CPP crystal identification—synovial fluid crystal analysis via compensated polarized light microscopy—is not an ideal gold standard for a number of reasons. Synovial fluid crystal analysis requires arthrocentesis, which is under-utilized in clinical evaluation of crystalline arthritis [20••]. Even more concerning, compensated polarized light microscopy may underdetect the presence of CPP crystals. Reasons include small size and relatively weak birefringence of CPP crystals compared with monosodium urate crystals, and variable expertise in interpreting polarized light microscopy [32•, 33]. A recent study using compensated polarized light microscopy additionally noted that the hallmark positive birefringence of CPP crystals was absent in nearly half of needle-shaped CPP crystals [34].

Requiring the demonstration of CPP crystals in synovial fluid for entry into clinical studies would severely limit the number of eligible patients, further hindering efforts to advance our knowledge of and treatments for this disease. In the ACR/EULAR 2015 Gout Classification Criteria, the presence of synovial fluid monosodium urate crystals in a symptomatic joint or bursa is sufficient for classification, although demonstration of these crystals is not required for gout classification. It remains to be seen whether the CPPD classification system will similarly provide a method for classifying clinical research subjects without requiring synovial fluid crystal analysis, while still maintaining a high degree of specificity for CPPD.

The limitations of compensated polarized light microscopy for CPP crystal identification raise questions about the role of a negative test in CPPD classification. In the 2015 ACR/EULAR Gout Classification Criteria, the absence of monosodium urate crystals in synovial fluid aspirate carries negative weight toward the total score (e.g., decreases the likelihood of classifying as gout) [27]. Assigning a negative weight to the absence of CPP crystals in synovial fluid aspirate may not be appropriate for CPPD, given the aforementioned challenges with crystal identification.

More sensitive methods for CPP crystal identification such as Raman spectroscopy, Fourier transform infrared spectroscopy, and lens-free polarized light microscopy are not widely available for clinical use [35]. A classification system must include tests that are available to most clinicians and investigators; if only a handful of individuals have access to tests that are important for classifying a disease, the criteria will lack sensitivity. Including these crystal identification techniques in a classification criteria system will likely be impractical.

A Role for Imaging Modalities in CPPD Classification

Imaging modalities provide an alternate method for identifying CPP crystals. In general, the sensitivity and specificity of imaging modalities to detect CPPD have been tested using synovial fluid CPP crystals identified by compensated polarized light microscopy as the gold standard. As discussed above, this represents an imperfect gold standard that creates difficultly with interpreting the performance of imaging modalities. Even if CPP crystals are definitively identified by imaging modalities, it will need to be determined whether CPPD can be classified based on imaging evidence alone, without joint pain.

X-ray chondrocalcinosis has sensitivity near 40% using synovial fluid CPP crystals as the reference standard [10–13]. Chondrocalcinosis specificity is thought to be high, although non-CPP calcium crystals can be responsible [4, 36]. Given the widespread use of x-ray in evaluating patients with possible CPPD, chondrocalcinosis will likely be included in the classification criteria system, and its relative importance for classification will be interesting to learn.

Ultrasound demonstrated high sensitivity (87%) and specificity (98%) for CPPD in a recent meta-analysis, although the same caveat about using synovial fluid CPP crystals as the reference standard holds true [14]. When ultrasound was interpreted at the patient level (e.g., results from all imaged joints, rather than a

single joint), sensitivity was 89% and specificity 94% [14]. Notably, the definition of a positive ultrasound slightly differed across studies. The Outcome Measures in Rheumatology (OMERACT) CPPD Ultrasound Subtask Force recently validated standardized definitions for ultrasound signs of CPP deposits [37••, 38]. These were then tested in a large prospective cohort of patients that all underwent synovial fluid crystal analysis, x-ray, and ultrasound of the knee [12]. The presence of ultrasound CPP deposits in the menisci, hyaline cartilage, and/or tendon had a sensitivity of 74% and specificity of 77% for CPPD, using synovial fluid CPP crystals as the reference standard. As CPPD classification criteria are developed, it is possible that ultrasound evidence in a single joint (e.g., knee) versus multiple joints will be assigned different weights.

Computed tomography (CT) accurately identifies calcific deposits in cartilage and intra-articular structures. Concordance of CT and x-ray for the presence of chondrocalcinosis in the knee was 100% in a subgroup of the Multicenter Osteoarthritis (MOST) Study [39]. CT images revealed calcium crystal deposition in the menisci (fibrocartilage) and hyaline cartilage, as well as the cruciate ligaments and joint capsule.

Conventional CT and x-ray are each limited by inability to distinguish between CPP versus hydroxyapatite. Dual-energy CT (DECT) incorporates data obtained from low- and high-energy beams to distinguish between materials of different chemical composition, such as different types of calcium-containing crystals. DECT images are post-processed to produce three-dimensional images indicating the location and total volume of crystalline deposits. DECT has demonstrated high sensitivity and specificity for detecting gout, and a small but growing number of studies in CPPD show it to be a promising modality that differentiates between CPP and hydroxyapatite [10, 16, 40]. To date, studies have not tested the sensitivity, specificity, and positive and negative predictive values of DECT in vivo in humans using synovial fluid CPP crystals as the reference standard.

Multi-energy spectral CT is a novel modality that has been tested for crystal identification (monosodium urate and CPP crystals) in cadaveric specimens [17]. It discriminates between CPP and hydroxyapatite crystals and, like DECT, provides quantification of the burden of deposits. While this modality seems promising, it is not widely available and is therefore unlikely to be included among classification criteria in the next few years.

Conclusions

Our ability to study outcomes in CPPD and develop treatments relies on developing a common understanding of what the disease involves. We must establish a uniform system for describing the disease to patients and among ourselves as clinicians and investigators. This will facilitate communication among providers and patients and will enhance EHR-based research. Development of a system for classifying CPPD is of paramount importance, as it will allow comparison of outcomes across studies.

Compliance with Ethical Standard

Conflict of Interest Sara K. Tedeschi is a member of the ACR/EULAR CPPD Classification Criteria team.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Abhishek A, Neogi T, Choi H, Doherty M, Rosenthal AK, Terkeltaub R. Review: unmet needs and the path forward in joint disease associated with calcium pyrophosphate crystal deposition. Arthritis & rheumatology. 2018;70:1182–91 **This review highlights challenges to advancing the research agenda in CPPD, including the lack of classification criteria**.
2. McCarty DJ, Kohn NN, Faires JS. The significance of calcium phosphate crystals in the synovial fluid of arthritic patients: the "pseudogout syndrome": I. clinical aspects. Ann Intern Med. 1962;56:711–37.
3. Kohn NN, Hughes RE, McCarty DJ, Faires JS. The significance of calcium phosphate crystals in the synovial fluid of arthritic patients: the "pseudogout syndrome". Ann Intern Med. 1962;56:738–45.
4. Rosenthal AK, Ryan LM. Calcium pyrophosphate deposition disease. N Engl J Med. 2016;374:2575–84.
5. Zhang W, Doherty M, Bardin T, Barskova V, Guerne PA, Jansen TL, et al. European League Against Rheumatism recommendations for calcium pyrophosphate deposition. Part I: terminology and diagnosis. Ann Rheum Dis. 2011;70:563–70.
6. Ryan L, McCarty D. Calcium pyrophosphate crystal deposition disease; pseudogout; articular chondrocalcinosis. In: McCarty D, editor. Arthritis and allied conditions. 10th ed. Philadelphia: Lea & Febiger; 1985. p. 1515–46.
7. McCarty DJ. Calcium pyrophosphate dihydrate crystal deposition disease: nomenclature and diagnostic criteria. Ann Intern Med. 1977;87:241–2.
8. Bursill D, Taylor WJ, Terkeltaub R, Kuwabara M, Merriman TR, Grainger R, et al. Gout, hyperuricemia, and crystal-associated disease network consensus statement regarding labels and definitions for disease elements in gout. Arthritis care & research. 2019;71:427–34.
9. van der Heijde D, Daikh DI, Betteridge N, et al. Common language description of the term rheumatic and musculoskeletal diseases (RMDs) for use in communication with the lay public, healthcare providers, and other stakeholders endorsed by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR). Arthritis & rheumatology. 2018;70:826–31.
10. Tanikawa H, Ogawa R, Okuma K, Harato K, Niki Y, Kobayashi S, et al. Detection of calcium pyrophosphate dihydrate crystals in knee meniscus by dual-energy computed tomography. J Orthop Surg Res. 2018;13:73.

11. Utsinger PD, Resnick D, Zvaifler NJ. Wrist arthropathy in calcium pyrophosphate dihydrate deposition disease. Arthritis Rheum. 1975;18:485–91.
12. Lee KA, Lee SH, Kim HR. Diagnostic value of ultrasound in calcium pyrophosphate deposition disease of the knee joint. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 2019;27:781–787.
13. Barskova VG, Kudaeva FM, Bozhieva LA, Smirnov AV, Volkov AV, Nasonov EL. Comparison of three imaging techniques in diagnosis of chondrocalcinosis of the knees in calcium pyrophosphate deposition disease. Rheumatology. 2013;52:1090–4.
14. Filippou G, Adinolfi A, Iagnocco A, Filippucci E, Cimmino MA, Bertoldi I, et al. Ultrasound in the diagnosis of calcium pyrophosphate dihydrate deposition disease. A systematic literature review and a meta-analysis. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society. 2016;24:973–81.
15. Gamon E, Combe B, Barnetche T, Mouterde G. Diagnostic value of ultrasound in calcium pyrophosphate deposition disease: a systematic review and meta-analysis. RMD Open. 2015;1:e000118.
16. Pascart T, Norberciak L, Legrand J, Becce F, Budzik JF. Dual-energy computed tomography in calcium pyrophosphate deposition: initial clinical experience. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society. 2019.
17. Stamp LK, Anderson NG, Becce F, Rajeswari M, Polson M, Guyen O, et al. Clinical utility of multi-energy spectral photon-counting computed tomography in crystal arthritis. Arthritis & rheumatology. 2019.
18. O'Malley KJ, Cook KF, Price MD, Wildes KR, Hurdle JF, Ashton CM. Measuring diagnoses: ICD code accuracy. Health Serv Res. 2005;40:1620–39.
19. Nigwekar SU, Solid CA, Ankers E, et al. Quantifying a rare disease in administrative data: the example of calciphylaxis. J Gen Intern Med. 2014;29(Suppl 3):S724–31.
20.•• Bartels CM, Singh JA, Parperis K, Huber K, Rosenthal AK. Validation of administrative codes for calcium pyrophosphate deposition: a Veterans Administration study. Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases. 2015;21:189–92 **This is the first administrative claims–based algorithm for CPPD**.
21. Kleiber Balderrama C, Rosenthal AK, Lans D, Singh JA, Bartels CM. Calcium pyrophosphate deposition disease and associated medical comorbidities: a National Cross-Sectional Study of US veterans. Arthritis Care & Research. 2017;69:1400–6.
22. Tedeschi SK, Solomon DH, Liao KP. Pseudogout among patients fulfilling a billing code algorithm for calcium pyrophosphate deposition disease. Rheumatol Int. 2018;38:1083–8.
23. Rho YH, Zhu Y, Zhang Y, Reginato AM, Choi HK. Risk factors for pseudogout in the general population. Rheumatology. 2012;51:2070–4.
24. Roddy E, Muller S, Paskins Z, Hider SL, Blagojevic-Bucknall M, Mallen CD. Incident acute pseudogout and prior bisphosphonate use: matched case-control study in the UK. Clinical Practice Research Datalink Medicine (Baltimore). 2017;96:e6177.
25. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the general practice research database: a systematic review. Br J Clin Pharmacol. 2010;69:4–14.
26. Aggarwal R, Ringold S, Khanna D, Neogi T, Johnson SR, Miller A, et al. Distinctions between diagnostic and classification criteria? Arthritis care & Research. 2015;67:891–7.
27. Neogi T, Jansen TL, Dalbeth N, et al. Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis & rheumatology. 2015;2015(67):2557–68.
28. Aletaha D, Neogi T, Silman AJ, et al. Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis and Rheumatism. 2010;2010(62):2569–81.
29. Tedeschi SK, Johnson SR, Boumpas DT, Daikh D, Dörner T, Diamond B, et al. Multicriteria decision analysis process to develop new classification criteria for systemic lupus erythematosus. Ann Rheum Dis. 2019;78:634–40.
30. Singh G, Lingala B, Mithal A. Gout and hyperuricaemia in the USA: prevalence and trends. Rheumatology. 2019.
31. Vargas-Santos AB, Taylor WJ, Neogi T. Gout classification criteria: update and Implications. Curr Rheumatol Rep. 2016;18:46.
32.• Berendsen D, Neogi T, Taylor WJ, Dalbeth N, Jansen TL. Crystal identification of synovial fluid aspiration by polarized light microscopy. An online test suggesting that our traditional rheumatologic competence needs renewed attention and training. Clinical Rheumatology. 2017;36:641–7 **This study identified that CPP crystals were less accurately identified than monosodium urate crystals via images from polarized light microscopy.**
33. Swan A, Amer H, Dieppe P. The value of synovial fluid assays in the diagnosis of joint disease: a literature survey. Ann Rheum Dis. 2002;61:493–8.
34. Andres M, Vela P, Jovani V, Pascual E. Most needle-shaped calcium pyrophosphate crystals lack birefringence. Rheumatology. 2019;58:1095–8.
35. Zell M, Zhang D, FitzGerald J. Diagnostic advances in synovial fluid analysis and radiographic identification for crystalline arthritis. Curr Opin Rheumatol. 2019;31:134–43.
36. McCarthy GM, Dunne A. Calcium crystal deposition diseases - beyond gout. Nat Rev Rheumatol. 2018;14:592–602.
37.•• Filippou G, Scire CA, Damjanov N, et al. Definition and reliability assessment of elementary ultrasonographic findings in calcium pyrophosphate deposition disease: a study by the OMERACT calcium pyrophosphate deposition disease ultrasound subtask force. J Rheumatol. 2017;44:1744–9 **This manuscript presents the OMERACT ultrasound definitions for CPPD in the fibrocartilage, hyaline cartilage, tendon, and synovial fluid**.
38. Filippou G, Scire CA, Adinolfi A, et al. Identification of calcium pyrophosphate deposition disease (CPPD) by ultrasound: reliability of the OMERACT definitions in an extended set of joints-an international multiobserver study by the OMERACT Calcium Pyrophosphate Deposition Disease Ultrasound Subtask Force. Ann Rheum Dis. 2018;77:1194–9.
39. Misra D, Guermazi A, Sieren JP, Lynch J, Torner J, Neogi T, et al. CT imaging for evaluation of calcium crystal deposition in the knee: initial experience from the Multicenter Osteoarthritis (MOST) study. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society. 2015;23:244–8.
40. Diekhoff T, Kiefer T, Stroux A, Pilhofer I, Juran R, Mews J, et al. Detection and characterization of crystal suspensions using single-source dual-energy computed tomography: a phantom model of crystal arthropathies. Investig Radiol. 2015;50:255–60.