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Unmet Needs and the Path Forward in Joint Disease Associated with Calcium Pyrophosphate Crystal Deposition

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Abstract

Calcium pyrophosphate (CPP) crystal deposition (CPPD) is prevalent, and can be associated with synovitis and joint damage. The older-aged population predominantly affected by CPPD is growing rapidly. Since shortfalls exist in many aspects of CPPD, we conducted an anonymous survey of CPPD unmet needs, prioritized by experts from the Gout, Hyperuricemia and Crystal-Associated Disease Network (G-CAN). We provide our perspectives on the survey results, and propose several CPPD basic and clinical translational research pathways. Chondrocyte and cartilage culture systems for generating CPP crystals *in vitro*, and transgenic small animal CPPD

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models are needed to better define CPPD mechanism paradigms and help guide new therapies. CPPD recognition, clinical research, and care would be improved by international consensus on CPPD nomenclature and disease phenotype classification, better exploitation of advanced imaging, and pragmatic new point-of-care crystal analytic approaches for detecting CPP crystals. Clinical impact of CPP crystals in OA, and in asymptomatic joints in the aged, remain major unanswered questions, rendered more difficult by current inability to therapeutically limit or dissolve the crystal deposits and assess consequent clinical outcome. Going forward, CPPD clinical research studies should define clinical settings in which articular CPPD does substantial harm, and include analyses of diverse clinical phenotypes and populations. Clinical trials should identify the best therapeutic targets to limit CPP crystal deposition and associated inflammation, and include assessment of intra-articular agents. Our perspective is that such advances in basic and clinical science in CPPD are now within reach, and can lead to better treatments for this disorder.

Keywords

calcium pyrophosphate; chondrocalcinosis; CPPD; crystal arthropathy; pseudogout; inorganic pyrophosphate; ENPP1; ANKH; TNAP

INTRODUCTION

Calcium pyrophosphate (CPP) crystal deposition (CPPD) in articular tissues is a prevalent disorder, and frequently associated with acute and chronic arthritis (1–4). The primary idiopathic disorder is by far the most common disease subtype and principally occurs in individuals over the age of 60 years, with progressive increases in prevalence with further aging (1, 3, 4). Osteoarthritis (OA), also a disease in which aging is a major risk factor, is commonly associated with CPPD (3). CPPD will grow as a public health problem, because the USA population over the age of 65 years is predicted to double to 89 million by the year 2050. CPPD also can develop prematurely in joints with prior injury, or in association with certain mutations and polymorphisms (1, 2, 4), and some uncommon metabolic disorders, such as hemochromatosis, hyperparathyroidism, hypomagnesemia, and hypophosphatasia (1, 4).

More than five decades after original CPPD characterization, there are major shortfalls in recognizing, understanding and specifically treating the disorder. When estimated by detection of radiographic chondrocalcinosis (CC), CPPD is common, affecting 0.42–0.52% of the general population (5, 6). Based on radiographic CC, CPPD can be estimated to affect approximately 8–10 million people in the USA (1). This estimate is conservative, as 25–50% of knee joints with synovial fluid CPP crystals lack radiographic CC (7), and advanced imaging using ultrasound and CT appear more sensitive for detecting CPPD than plain radiography (8–11). Lack of specificity of CC on conventional radiography for CPPD is another consideration, when estimating CPPD prevalence (1, 4). In addition, accurate detection of CPP crystals in synovial fluids is challenging, with considerable inter-observer and inter-institutional variability (1). Furthermore, we lack international consensus for disease nomenclature and classifications (1, 12), with inaccurate international classification

of diseases (ICD) coding terminology for CPPD itself and CPPD disease phenotypes as one consequence. All these factors hamper recognition and study of CPPD.

Here, we surveyed crystal-associated arthritis experts on prioritization of CPPD unmet research needs. We utilized the membership of the Gout, Hyperuricemia and Crystal-Associated Disease Network (G-CAN). Established in 2014, this international group of rheumatologists, nephrologists, and non-clinical scientists share interest and expertise in crystal arthropathies. We present and provide our own perspectives on the results of the expert survey and the CPPD field at large. In doing so, we suggest and expand upon potentially productive pathways for future basic, clinical, and translational research in CPPD.

METHODS

CPPD Research prioritization survey

We conducted web-based survey of G-CAN membership of CPPD research priorities. Survey questions, developed by the fist author, and the senior authors of this paper, and listed in Supplementary Material, Table 1, were e-mailed to academic and clinical practice-based clinician and non-clinician PhD attendees of 2015 and/or 2016 G-CAN annual symposia. Invited participants were from 27 countries in Asia, Europe, Oceania, North and South America. They were asked to anonymously rate research priorities using a 5-point Likert scale, with responses ranging from 1–5: (5: Very important research priority; 4: Important research priority; 3: Moderately important research priority; 2: Lesser research priority; 1: Not a research priority). The CPPD domains addressed were: clinical phenotyping, diagnostic modalities, pathogenesis, stratified medicine, outcomes, and treatment. Responses were categorized as: (i) Highest priorities (4–5 on the scale), as rated by >80% of respondents; (ii) Medium priorities (rated 4–5), but ranked so according to only 66.7–80% of respondents; Lower priorities (rated 4–5), but ranked so by fewer than 66.7% of respondents.

RESULTS

Twenty-six surveys were completed, from a total of 140 invited participants. Responders were residents of ten countries across four continents; 79.3% were physicians. G-CAN member survey respondents rated the 8 highest research priorities (Table 1). In the pathogenesis domain, better definition of the mechanisms by which CPPD develops in joints with and without OA, and identification of basic mechanisms and other factors causing acute arthritis in CPPD, including flare triggers, were selected as important research priorities. For detection and diagnosis, respondents deemed development of improved analytic techniques for CPP crystal detection in tissues, and advanced imaging modalities for affected joints, as high priorities. Clearer phenotyping of arthropathies associated with CPPD, and identification of people likely to benefit from reducing CPPD were regarded as important research priorities in the domain of clinical phenotyping and stratified medicine. For therapy, identification and testing new approaches that effectively prevent, limit and/or reverse CPPD, and evaluation of the efficacy and safety of currently used pharmacologic agents in acute and chronic CPP crystal arthritis, were identified as important research priorities.

DISCUSSION

Experts in crystal-associated arthritis, surveyed on CPPD unmet needs, identified several high priority areas for research in this prevalent disorder. For each study area, there were limitations due to the low frequency of survey respondents, and the constrained breadth and depth of the survey questions. Hence, we expanded on the survey results with our own perspectives, and proposed specific research pathways to move forward, as detailed below for prioritized research areas.

Survey results for CPPD pathogenesis in context of current knowledge

How CPPD develops in joints—Recent reviews have detailed the current understanding of the processes of CPP crystal deposition (47–51) and CPP crystal-induced acute inflammatory arthritis (1, 4). To summarize, it is well-recognized that CPP crystals deposit almost exclusively in articular hyaline cartilage and fibrocartilage, and at sites of chondroid metaplasia, including in the synovium (13, 14). Calcifications also occur in tendons of joints affected by CPPD but it remains unclear if these are comprised of basic calcium phosphate (BCP) or CPP crystals, or both (15). As reviewed elsewhere, CPP crystal formation in cartilage is promoted by substantial effects of alterations in chondrocyte differentiation and function, such as chondrocyte hypertrophy and autophagy, altered properties of articular cartilage secretory vesicles, and changes in extracellular matrix composition and solutes, including magnesium, which suppresses CPP crystal formation (1, 4). General effects of aging on articular cartilage, particularly including effects on inorganic pyrophosphate (PP_i) metabolism in CPPD (16–18), likely modulate multiple aspects of CPPD. We have well-developed understanding of how altered PP_i generation, transport, and degradation regulate CPP crystal deposition (1–4). PP_i is generated intracellularly and extracellularly from ATP and other nucleoside triphsposphates by the ecto-enzyme ectonucleotide pyrophosphatase phosphodiesterase 1 (ENPP1) (1, 4). Approximate doubling of both cartilage ENPP activity and PP_i have been reported in idiopathic CPPD, compared to normal cartilages (4). The ecto-enzyme TNAP degrades soluble PP_i to P_i, and *in vitro*, TNAP can degrade CPP crystals (19). In adult hypophosphatasia, where TNAP activity is deficient, premature onset CPPD can develop (1, 4). In joint cartilages with OA, the common co-existence of CPP and BCP crystal deposits is likely mediated by coupling of increased PP_i production and PP_i hydrolysis (4).

ANKH, a multiple-pass transmembrane protein, plays a central role in transporting PP_i to the cell exterior, and appears to play a direct or indirect role in ATP export from cells (1, 2, 4). A variety of *ANKH* mutations have been implicated in familial CPPD, but with distinctions in clinical phenotypes based on the different sites in mutations (1, 2, 4). Homozygosity for −4 G to A substitution in the *ANKH* 5-untranslated region, which promotes increased *ANKH* expression *in vitro*, has been shown to be present in 4% of ~4 patients presenting with late onset CPPD (20, 21). Significantly, ENPP enzymatic activity and ANKH levels in chondrocytes, and joint fluid PP_i, also are elevated in aging and OA cartilages (4).

How CPP crystals promote arthritis and joint damage—CPP crystals in cartilage can traffic within the joint, and directly stimulate cellular inflammatory responses (1, 4). Multiple mechanisms by which CPP crystals promote inflammation and cartilage matrix catabolism have been identified by concurrent study of urate crystal-associated inflammation (4, 22). Examples are NLRP3 inflammasome activation and IL-1β release, cell stress and inflammation signal transduction pathways, production of prostaglandins and leukotrienes, and of cytokines including TNFα and chemokines (1, 4, 22). However, increased intracellular calcium, due to phagolysosomal degradation of ingested CPP crystals, likely activates signalling pathways distinct from those stimulated by urate crystals (23). The capacities of CPP crystals to stimulate expression of MMPs and synovial fibroblast proliferation are germane to development of arthritis in CPPD (1, 4).

Our suggested path forward in CPPD pathogenesis

Progress in understanding CPPD pathogenesis would be furthered by coordinated international efforts, with translational emphasis (Table 2). For example, lessons on disease pathogenesis from secondary CPPD due to metabolic diseases could advance understanding of CPPD pathogenesis at a population level, and lead to potential new prevention and treatment approaches. A role for iatrogenic factors in secondary CPPD may be substantial at the population level, exemplified by hypomagnesemia promoted by proton pump inhibitors, loop and thiazide diuretics, calcineurin inhibitors, and bowel resection (3). In addition, prevalence of idiopathic CPPD in populations could vary due to differences in calcium intake (24) (by modulation of PTH levels, and other alterations in other calciotropic hormones, vitamins, and growth factors), and distinctions in magnesium intake and metabolism (25).

We clearly need better, unifying disease models for CPPD with and without clinically important OA. In an emerging model of primary CPPD, a systemic disorder of calcification is posited that affects articular and non-articular tissues (15, 26, 27). Specifically, subjects with CC had overall decreased cortical bone mineral density, and elevated frequency of vascular calcification and other soft tissue calcification compared to controls (26). In other datasets CPPD associated with osteoporosis and with bisphosphonate prescription (26–28). Understanding unique characteristics of patients with knee OA with and without CPPD should lead to improved insight into OA pathogenesis, and how CPPD contributes to OA, as well as identification of potential therapeutic targets.

Huge gaps in the CPPD field include lack of chondrocyte and cartilage organ culture systems, and transgenic animal modelling of CPPD, where CPP crystals are precipitated *in vitro* and *in vivo*, respectively, by whole cells and tissues under physiologic conditions. Advances in this area would greatly help in identifying and testing potential new therapies. Unexpectedly, GWAS and other epigenetics research of cohorts with primary CPPD, especially looking at those with clinically manifest joint disease, were not rated as a particularly high priority in the G-CAN survey. GWAS may not have been applied to idiopathic CPPD because of a disease model disproportionately emphasizing the effects of aging. Clearly, aging alone cannot explain the fact that CPPD prevalence appears to vary widely between populations. For example, there is far lower age-standardized prevalence in

Beijing Chinese compared to White Americans in the USA, despite the fact that knee OA is more common in women in China (24). Phenotypic heterogeneity of kindreds with familial CPPD, even with mutations limited to *ANKH* (29), could allow genomics to potentially illuminate idiopathic and OA-associated CPPD pathogeneses. Examples include kindreds with mixed phenotypes of CC and features such as premature OA, spondyloephyseal dysplasia, and skeletal deformities and hyperostosis (30). Genetic linkages to mutation of *TNFRSF11B* (that encodes osteoprotegerin) (31) and procollagen II (32) have been reported in some such kindreds with CPPD.

Survey results for CPPD detection, diagnosis, and classification in context of current knowledge

Top priorities identified, in the diagnostics domain, included development of improved analytic techniques for detection of CPP crystals in tissues and synovial fluids, and continued refinement of advanced imaging modalities.

Current status of CPPD detection, classification, and diagnosis—It remains problematic that CPPD diagnostic criteria lack validation and international consensus. Importantly, CPP crystal detection and imaging reference standards, not symptomatic arthritis, are used to delineate definite or probable disease (33). Contrast to classification of another crystal-associated arthritis, gout, is potentially instructive. Specifically, gout classification, including by the 2015 ACR/EULAR criteria, has been jointly based on classical clinical features of gouty arthritis, coupled with detection of urate crystal deposition (34). Detection of urate crystal deposits by advanced imaging is a common finding in asymptomatic hyperuricemia (121–123). In contradistinction to CPPD, urate crystal deposition is not sufficient to classify such a disorder as a crystal-associated arthritis.

Presence of CPP crystals in synovial fluid of an affected joint is perhaps the most stringent definition of CPPD. Unfortunately, the detection of CPP crystals is notoriously inaccurate (35). Variability in morphology, birefringence characteristics, and the small size and relative sparseness of CPP crystals in joint fluid can render their detection quite challenging (36, 37). Use of conventional radiography to detect CC is not an ideal screening tool. Without adequate validation of a protocol for the extent and number of loci examined, using conventional radiographs to detect CC will result in under-recognition of clinically important CPPD.

Our suggested path forward in detection and diagnostic classification of CPPD

The path towards more accurate CPPD diagnosis (Table 2) should involve the development of uniform, and internationally standardized classification criteria, similar to those arising from the 2015 ACR/EULAR effort for gout (34). In gout, synovial fluid crystal analysis remains the gold standard in diagnosis, but ultrasound and dual energy CT (DECT) are weighted equally with palpable tophus detection in ACR/EULAR diagnostic criteria (34). Prospective, randomized, blinded clinical trials of new diagnostic approaches, with comparison to reference standards (compensated polarized light microscopy, sensitive and specific imaging) are needed in CPPD. Ideally, there would be inclusion of studies in real-world clinical practice scenarios, where patients are referred for clinical diagnosis.

Traditionally, analytic methods for definitively analyzing crystal composition such as electron microscopy, x-ray diffraction, Raman spectroscopy, and Fourier-transform infrared (FTIR) spectroscopy have been expensive, and not generally available in clinical settings. Recent work illuminates the potential of modifying these crystal identification approaches for accessible clinical use. Point-of-care Raman spectroscope (POCRS), involving a shoebox-sized device is one example (38). Use of a lens-free polarized microscope, for wide field of view, high-resolution holographic imaging of birefringent objects, also appears sensitive and specific for detecting urate crystals in joint fluids (39). Both of these approaches need to be validated for synovial fluid CPP crystal analysis.

Currently, high resolution ultrasound, DECT, and potentially new iterations of MRI, are at the leading edge of advanced imaging approaches to CPPD detection (8–10). Further imaging studies using each modality will be needed to replicate prior findings on characteristics of CPPD using conventional radiography. DECT has undergone only minimal evaluation specifically in CPPD (in comparison to broad evaluation in gout). In contrast, multiple analyses of ultrasound have used conventional crystal analyses or conventional radiography as reference standard in CPPD (8, 10). Both a EULAR expert panel, and a systematic review with statistical analysis, concluded that ultrasound was superior in sensitivity to conventional radiography for CPPD (12). However, internationally accepted protocols, standards, and consensus for ultrasound imaging patterns highly specific for tissue CPPD deposits are lacking. Each new diagnostic approach for CPP crystal analyses and detection by imaging would ideally be integrated into international consensus to generate uniform diagnostic criteria for CPPD.

Survey results for CPPD clinical phenotyping and stratified medicine in context of current knowledge

An identified top research priority was to improve phenotyping of inflammatory and non-inflammatory arthropathies associated with CPPD. Interestingly, better understanding of the difference between OA with CPPD and chronic CPP crystal arthritis, and the impact of CPPD on outcomes of OA were identified as only moderately important research priorities.

Current status of CPPD clinical phenotyping—McCarty and Ryan first proposed a CPPD classification scheme based on various clinical presentations, which they named as mimics of other diseases, such as “pseudogout”, and “pseudorheumatoid arthritis, or “lanthanic” (ie, asymptomatic) disease (40). More recently, EULAR advanced a CPPD classification system and nomenclature system (12). No clinical phenotyping scheme has been validated. Clinical significance, and impact on OA, of incidentally-noted radiographic CC has not been established by direct study. The relationship between arthritis due to acute and chronic forms of CPPD is not fully understood (12). Furthermore, the place in CPPD classification remains unclear for other presentations of CPPD (eg, “crowned dens syndrome”, pseudotumoral CPPD masses, polymyalgia rheumatica-like pain syndromes, mixed crystal deposition, and acute CPP crystal arthropathy early and late after knee arthroplasty)(1, 4).

A recent study suggested CC to be associated with increased pain but not MRI-assessed synovitis in knee OA (41). While some studies suggest that CPP crystal deposits do not accelerate knee OA progression (42), others suggest that CC produces greater radiographic attrition, a distinct pattern of joint involvement, and rapid progression of structural knee arthropathy (43–46). Clearly, the field is held back by enigmatic lines and shadings between CPPD and various forms of degenerative joint disease, such as OA, including OA and mixed CPPD and BCP crystal deposition (11).

Our suggested path forward in CPPD clinical phenotyping and stratified medicine

Past emphasis on clinical phenotyping in CPPD, via primary sourcing of the majority of the cases from hospital-based rheumatologists, may have skewed clinical presentations of this disease to more severely affected individuals. As such, the path to address research priorities in this domain (Table 3) should ideally include large, multi-center studies, based in settings including the community at large. In this way, we can better discern frequency, distribution and severity, and natural course of clinical phenotypes of CPPD, especially for chronic arthopathy due to CPPD. Greater appreciation of the natural history of these clinical subtypes will be critical to determine the nature, frequency, and outcomes specific to different CPPD phenotypes in long-term studies, and the frequency of significant cross-over of one phenotype to another. Collectively, such works would help in launching prospective clinical trials in CPPD.

Untangling the complex relationship between OA and CPPD will take careful delineation of hypotheses, and would benefit from application of cutting edge genomic and molecular approaches in articular cells. Chondrocyte molecular signatures that promote pathologic calcification will be particularly informative to define in CPPD. This is particularly so because CPPD is associated with modifications of the radiographic OA phenotype. Specifically, CPPD appears linked with decreased metacarpal cortical bone density, potentially mediated in part by dysregulated PP_i metabolism (26). Moreover, in a study of severe symptomatic large joint OA, there was a milder imaging phenotype of hip OA linked with CPPD assessed by plain radiography (45), and this work needs validation in a larger cohort. There are challenges raised by the fact that advanced hip OA, with attendant cartilage loss, renders visualization of CC more difficult. Prospective, longitudinal studies will be needed to determine if OA is truly a risk factor for CC, and whether CC and/or CPPD adversely affects the progression, severity or outcomes of OA.

Better defining the clinical phenotype(s) of chronic inflammatory polyarthritis in CPPD will be necessary for designing clinical treatment trials for these patients. In this context, we need to know if this phenotype reflects qualitative rather than quantitative and topologic aspects of CPP crystal deposition, such as presence of more pro-inflammatory monoclinic CPP crystals relative to triclinic CPP crystals(47). We also need to better define what host factors mediate the chronic, and frequently RA-like, phenotype of polyarticular proliferative synovitis.

Survey results for treatment

The impact of CPP crystals in OA, and in asymptomatic joints in the aged, remain large, unanswered questions, made more difficult by our current inability to limit or dissolve the crystal deposits and assess consequent clinical outcome. Accordingly, the survey identified advances in methods to prevent, limit and/or reverse CPPD as the top research priority (Table 3). Similarly, the need to evaluate the efficacy and safety of various drugs in acute and chronic CPP crystal arthritis and identification of people likely to benefit from reducing CPPD were deemed high research priorities.

Current state of knowledge for CPPD treatment—Anti-inflammatory strategies are central to treatment of acute CPP crystal arthritis (48). However, unlike treatment of acute gout, there is paucity of high quality research trial data specific to management of acute CPPD arthritis. For instance, evidence supporting the use of colchicine for prophylaxis of flares of recurrent acute CPP crystal arthritis is limited to a single study of 10 CPPD patients (49). Systemic and intra-articular corticosteroids (50) (recommended by EULAR on the bases of expert opinion) (48), ACTH (51), and anakinra (52, 53), can be employed for treatment of acute CPP crystal arthritis, but using regimens largely adapted from those for acute gout.

Treatment of chronic arthritis in CPPD is currently centred on inflammation and symptom control. Intra-articular corticosteroid injections for large joint arthritis, low dose systemic corticosteroids, colchicine for acute arthritis (54) and chronic inflammatory arthritis, and NSAIDs are commonly employed (48). Hydroxychloroquine (55) and methotrexate (56, 57) have been studied for treatment of chronic inflammatory polyarthritis due to CPPD, and there is scientific rationale for both drugs in crystal-induced inflammation (23, 58). Published experience with hydroxychloroquine and methotrexate has primarily been from small case series of clinically heterogeneous patients. Recently, a small, double-blind, crossover controlled trial of methotrexate (15 mg/week) randomized 26 patients, comparing 25 treatment periods of 3 months on methotrexate with 21 treatment periods of equal lengths on placebo (59). Inclusion criteria, for patients with crystal-proven CPPD, were clinical phenotypes of either recurrent arthritis or chronic polyarthritis, with failure of NSAIDs, corticosteroids, or colchicine. Neither pain nor disease activity scores (based on arthritis in 44 joints) were significantly different with methotrexate compared to placebo (59). However, the study may not have been adequately powered to detect meaningful differences between groups.

Methods to dissolve articular CPPD crystals, such as local administration of polyphosphates, tissue-nonspecific alkaline phosphatase (TNAP), or calcium chelators have not gained traction. This approach can trigger marked, acute flares of arthritis, presumably due to liberation of CPP crystals from cartilage.

Our suggested path forward for CPPD treatment

Strategies for testing existing and emerging anti-inflammatory drugs in acute CPP crystal arthritis should be tailored to distinct clinical features of CPPD (e.g. frequent large joint acute arthritis, and chronic symmetric inflammatory synovitis). Nevertheless, emerging

approaches to experimental urate crystal-induced inflammation could be adapted from the gouty arthritis pipeline.

In gout, successful achievement of sustained hypouricemia is highly effective in resolving urate crystal deposits (60). Hence, CPP crystal deposits could, in theory, be similarly limited by robustly decreasing systemic extracellular PP_i levels. However, a large body of evidence suggesrs caveats in developing drugs for CPPD that potently decrease systemic extracellular PP_i. Specifically, certain cell types, including chondrocytes and vascular smooth muscle cells and aortic valve cells, limit pathologic extracellular matrix calcification in part by physiologic release of PP_i (61–63). Deficiencies in ENPP1 and ANKH, and TNAP excess, promote pathologic calcification in arteries and other soft tissues, and metabolic bone disease (64–66). Murine genetic ENPP1 haploinsufficiency also increases vascular smooth muscle cell proliferation and accelerates arterial injury-induced neointimal hyperplasia *in vivo* (67). As such, it would be helpful to define if CPPD reflects a systemic excess in tissue PP_i levels that can be therapeutically tuned back to normal, or, alternatively, widespread extracellular PP_i excess in articular tissues with normal extracellular PP_i levels in nonarticular tissues. Clearly, intra-articular delivery of long-acting therapeutics should be considered among the approaches for evaluation in CPPD, particularly in large joint arthritis.

Oral magnesium supplementation limits CPP crystal formation and potentially could improve dysregulated PP_i metabolism in CPPD (68). Recent work supports studying magnesium supplementation even at normal levels of serum magnesium (25). Insulin-like growth factor-I (IGF-I) promotes decreased extracellular PP_i, partially by antagonizing TGFβ effects on chondrocyte differentiation and function (69). However, the effect of impaired IGF-I signalling responses in aging and OA chondrocytes on potential efficacy of articular IGF-I administration is unclear (70). Decreased mitochondrial function promotes dysregulated PP_i metabolism, by effects including impairment of ATP synthesis and possible compensatory increase in extracellular adenine nucleotide scavenging (71, 72). Significantly, dysregulated mitochondrial function is emerging as a drug target for diseases of aging, including OA (73), and may provide a niche for potential CPPD therapy development. Purinergic receptpr signalling also has been identified as a potential target in CPPD (74). Developing and validating testing for systemic and articular PP_i metabolism, at the clinical laboratory level, would help exploit the therapeutic potential of ANKH inhibitors and other PP_i transport and metabolism modulators for precision medicine in CPPD (29, 74).

Last, in addition to carefully identifying a homogenous study population, there are other obstacles to the design and execution of prospective, randomized clinical therapy trials in CPPD. Recruitment for a disease that is not well understood by non-rheumatologists will be challenging. Elderly patients frequently have multiple co-morbidities that may complicate drug studies. There are added challenges in choosing comparator drugs for a disease with no FDA-approved therapies.

Conclusion

Conclusions of the CPPD consensus and review processes presented here particularly emphasized the need to study the disorder more in the population at large. Clearly, the

capability to therapeutically limit or dissolve the crystal deposits, and assess consequent clinical outcome, would greatly enhance our ability to conclusively define the clinical impact, and long-term effects on joint function of CPP crystals in OA, and in asymptomatic joints in the aged. Fortunately, better addressing unmet needs in CPPD is more feasible than in previous decades. The effort should merge multiple investigative paths, starting with a better understanding of pathogenesis that increases precision in management. Of further help would be development of internationally standardized nomenclature and classification of disease, to more clearly separate CPPD phenotypes that are asymptomatic, symptomatic, and likely to promote synovitis and joint damage. Emerging advanced imaging and crystal analytic diagnostic approaches are now available for broader application to CPPD. Thoroughly defining clinical settings in which articular CPPD does substantial harm will be an important aspect of designing new clinical trials for the disorder. Caveats in potently decreasing systemic extracellular PP_i should be considered in developing safe and effective CPPD therapies. It would be important to assess not only conventional agents, but also novel and selective molecular anti-inflammatory agents, in well-designed clinical trials for CPPD-associated inflammatory arthritis. Use of intra-articular long-acting agents could be useful in limiting not only CPP crystal deposition but also associated synovitis, particularly for large joint disease. The path forward in CPPD would benefit from international collaborative studies. Timing for such work is fitting for the ultimate goal of improving the lives of patients with arthritis associated with CPPD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1
Results of G-CAN member survey on CPPD

The following CPPD domains were addressed: CP: clinical phenotyping, D Detection & Diagnosis: P: pathogenesis, SM: stratified medicine, O: outcomes; T: treatment.

Research priority (domain[1])	% rating ≥ important
Identify and test new approaches for preventing, limiting and/or reversing CPPD (T)	96%
Develop improved analytic techniques for detection of CPP crystals in tissues, including pragmatic point-of-care systems (D)	92%
Better definition of the mechanisms by which CPPD develops in joints with and without OA (P)[2]	88%
Develop advanced imaging modalities for improved detection of intra-articular CPPD (D)	85%
Evaluate efficacy and safety of colchicine, corticosteroids, disease-modifying anti-rheumatic drugs, and cytokine antagonists in acute and chronic CPP crystal arthritis (T)	85%
Improve phenotyping of inflammatory and non-inflammatory arthropathies associated with CPPD (CP)[2]	84%
Identification of basic mechanisms and other factors causing symptomatic acute arthritis in CPPD, including its' triggers (P)	81%
Identify people likely to benefit from reducing CPP crystal deposition (SM)	81%
Define precise clinical relationship between primary CPPD with non-inflammatory arthritis, and OA with CPPD (CP)	77%
Better define the impact of CPPD on the outcome of OA (O)	77%
Identify mechanisms causing chronic arthritis and damage in CPPD (P)[2]	76%
Understand the natural history of CPPD, including changes in clinical phenotype and transition to symptomatic CPPD (O)	73%
Identify patients who would benefit from reducing CPP crystal-induced inflammation (SM)	69%
Identify genetic and epigenetic factors in idiopathic CPP crystal arthritis (P)	62%
Identification of risk factors for CPPD (P)	62%
Identify biomarkers of development of CPPD (SM)[2]	52%
Identify people with CPPD for whom screening for metabolic diseases is appropriate (SM)[3]	48%
Evaluate effect of CPPD on outcomes of arthroplasty (O)[3]	39%

[1] Domains assessed: CP: clinical phenotyping, D Detection & Diagnosis: P: pathogenesis, SM: stratified medicine, O: outcomes; T: treatment;

[2] 25 completed responses;

[3] 23 completed responses.

Table 2

Author suggestions for pathways to address unmet needs in CPPD pathogenesis, detection and diagnosis:

- Advance understanding of factors that increase PP_i generation and release, modify PP_i degradation, and modulate CPP crystal deposition in articular connective tissues:
  - Development and validation of chondrocyte and cartilage culture systems, and transgenic animal modelling of CPPD, to advance identification and testing of potential new therapy targets
- Better define environmental, diet and lifestyle, and iatrogenic factors influencing CPPD at population levels, ideally using international consortia
- Genomics and “multi-omics” studies of primary CPPD with clinically manifest disease, including different races and ethnicities
- Generate a better, unifying disease model (or models) for primary CPPD with and without clinically manifest disease:
  - Model 1: (?) Systemic disorder of calcification expressed only in articular and periarticular tissues predisposed to generate and/or alternatively transport more PP_i (and possibly also ATP) in aging
  - Model 2: (?) Systemic disorder of abnormal calcification expressed in articular tissues, various soft tissues and arteries, and with metabolic bone disease

CPP crystal detection and diagnosis

- Uniform, internationally standardized nomenclature and classification criteria for CPPD, emphasizing clearer lines between the asymptomatic CPPD disorder, OA with CPPD, and unique symptomatic disease phenotypes
- Prospective, randomized, blinded clinical trials of new diagnostic approaches, with comparison to reference standards (compensated polarized light microscopy, plain radiography)
- Inclusion of studies in real-world clinical practice scenarios, where patients are referred for clinical diagnosis
- Development of point-of care crystal identification approaches, adapting highly specific analytic modalities for portability and cost-effectiveness (eg, Raman spectroscopy, lens-free polarized microscopy with wide field of view, high-resolution holographic imaging of birefringent objects)
- Further advanced imaging studies for CPPD, with development of internationally accepted protocols and standards

Table 3

Author suggestions for pathways to address unmet needs in CPPD clinical phenotyping and stratified medicine, and treatment: CPPD clinical phenotyping and stratified medicine

- Clinical CPPD phenotyping and natural disease course studies that include:
  - Large, multi-center studies, based in the community at large, and diverse consortia
  - Longitudinally studying asymptomatic CC at baseline
  - Better defining clinical phenotypes in chronic CPPD inflammatory polyarthritis, including host inflammatory response factors and qualitative and quantitative aspects of CPP crystal deposition
- Better defining the complex relationship between OA and CPPD, and using longitudinal studies and diverse consortia
- Thoroughly defining clinical settings in which articular CPPD does substantial harm

CPPD treatment:

- Limiting and reversing CPP crystal deposition (eg, by modulation of PP_i metabolism, and potentially certain solutes, chondrocyte growth factors, and calciotropic and extracellular matrix factors)

  In developing and testing such therapeutics:
  - Advance and validate testing for systemic and articular PP_i metabolism at the clinical laboratory level to promote precision medicine
  - Assess for possible limiting toxicity in bone and arteries of systemic PP_i lowering
  - Include study of intra-articular approaches
- Strategies for testing existing and emerging anti-inflammatory drugs in acute CPP crystal arthritis should be adapted to distinct clinical features of CPPD (eg, frequent large joint acute arthritis, and chronic symmetric synovitis)
- Test emerging approaches effective in experimental crystal-induced inflammation (eg, NLRP3 inflammasome inhibitors)
- Design CPPD therapy trials to overcome natural limitations in recruitment and to select appropriate active comparator