associated (see supplementary Table S2, available at *Rheumatology* online). Only one of four patients with late gadolinium enhancement focal fibrosis had abnormal baseline EP testing.

These data reveal that those developing significant arrhythmias over 3 years were more likely to have (multiple) abnormal EP tests at baseline, with abnormal findings associated with higher serum cardiac biomarkers. This is consistent with our published primary analysis where ILR-detected significant arrhythmias were associated with higher baseline cardiac biomarkers [4].

Although a pilot study with a small number of patients and not powered to show statistical differences, these findings suggest that a composite of non-invasive EP investigations, serum cardiac biomarkers and CMR could inform the use of ILR to pre-empt scleroderma heart disease-associated arrhythmias and reduce associated mortality.

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Lesley-Anne Bissell[1,2,*], Raluca B. Dumitru[1,2,*], Bara Erhayiem[3], Giuseppina Abignano [1,2], Graham Fent[3], Ananth Kidambi[3], Helena Donica[4], Agata N. Burska [1,2], Francesco Del Galdo[1,2], John Biglands[2], John P. Greenwood[3], Sven Plein [3], Lee Graham[5] and Maya H. Buch[1,2]

[1]*Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds,* [2]*NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust,* [3]*Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK,* [4]*Department of Biochemical Diagnostics, Medical University of Lublin, Lublin, Poland and* [5]*Department of Cardiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK*

*Lesley-Anne Bissell and Raluca B. Dumitru contributed equally to this study.

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Correspondence to: Maya H. Buch, Leeds Institute of Rheumatic and Musculoskeletal Medicine, Chapel Allerton Hospital, Chapeltown Road, Leeds LS7 4SA, UK.
E-mail: m.buch@leeds.ac.uk

Supplementary data

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A prospective study of dual-energy CT scanning, US and X-ray in acute calcium pyrophosphate crystal arthritis

Rheumatology key message

- Dual-energy CT demonstrated excellent sensitivity for acute calcium pyrophosphate crystal arthritis.

Dear Editor, CPPD crystal deposition disease, a common inflammatory arthritis, is notoriously underdiagnosed [1, 2]. Acute calcium pyrophosphate (CPP) crystal arthritis typically presents as acute monoarthritis, representing the most dramatic subtype of CPPD [2]. The CPPD diagnostic criteria proposed >30 years ago require both demonstration of CPP crystals in synovial fluid and X-ray chondrocalcinosis [3]. US and dual-energy CT (DECT) have been adopted for use in crystalline arthritis diagnosis and research since these CPPD diagnostic criteria were proposed. US is highly sensitive and specific for CPPD and demonstrates high inter-observer reliability [4, 5]. DECT can distinguish CPP from monosodium urate crystals and demonstrates high sensitivity and specificity for CPPD in *ex vivo* meniscectomy samples [6, 7]. We performed a pilot study to assess the sensitivity of DECT for acute CPP crystal arthritis as compared with US and X-ray.

Table 1 Presence and location of radiographic outcomes in the aspirated joint

Subject	DECT colour-coded changes (cm^3)	Conventional CT chondrocalcinosis	US calcific deposits	X-ray chondrocalcinosis
1	Patellofemoral Post. superior femoral condyle Meniscus Tibiofibular (0.48)	Patellofemoral Post. superior femoral condyle Meniscus	Meniscus	Meniscus
2	Intercondylar notch Meniscus (0.73)	Meniscus	Femoral cartilage Meniscus	Meniscus
3	Intercondylar notch Meniscus Patellofemoral Tibiofibular (2.85)	Intercondylar notch Meniscus Patellofemoral Post. superior femoral condyle Tibiofibular	Femoral cartilage	Intercondylar notch Meniscus Patellofemoral
4	Intercondylar notch Meniscus Patellofemoral Post. superior femoral condyle Popliteus tendon insertion Quadriceps tendon (1.05)	Meniscus Patellofemoral Post. superior femoral condyle Popliteus tendon insertion Quadriceps insertion	Femoral cartilage	Meniscus
5	Meniscus Post. superior femoral condyle Quadriceps tendon (0.50)	Meniscus Post. superior femoral condyle	Femoral cartilage	Meniscus Patellofemoral
6	Meniscus Patellofemoral (0.67)	Meniscus Patellofemoral	Femoral cartilage	None
7	Meniscus Patellofemoral Post. superior femoral condyle (1.33)	Meniscus Patellofemoral Post. superior femoral condyle	Femoral cartilage Meniscus	Meniscus Patellofemoral
8[a]	Intercarpal (0.02)		Intercarpal TFCC	None
9	Meniscus (0.45)	Meniscus	Meniscus	None
10	1st CMC Intercarpal 1st to 5th MCP TFCC (0.82)	1st CMC Intercarpal 1st to 5th MCP Radiocarpal TFCC	TFCC	Intercarpal 1st to 2nd MCP Radiocarpal TFCC

[a]Right wrist was both the aspirated and standardized joint. TFCC: triangular fibrocartilage complex.

We identified eligible patients at an academic medical centre, from March to November 2018, and reviewed the electronic medical record for the following entry criteria: age $\geqslant$18 years; acute monoarthritis of the wrist, hand, elbow, knee, ankle or foot; and recent arthrocentesis with synovial fluid crystal analysis positive for CPP crystals. Patients were ineligible if synovial fluid crystal analysis was positive for both monosodium urate and CPP crystals; surgical hardware was present in the aspirated joint; pregnant; unable to lie flat; or weight was $\geqslant$204 kg. The Partners HealthCare Institutional Review Board approved this study and patients provided informed consent prior to study procedures.

The study visit occurred as soon as possible after joint aspiration. Subjects completed a questionnaire regarding the current episode and underwent DECT, US and X-ray of the aspirated joint and a standardized joint (right wrist) following a standardized protocol (see supplementary material, section on Imaging modalities, protocols, and DECT software settings, available at *Rheumatology* online). The primary DECT outcome was presence of colour-coded changes indicating CPP deposits. We considered two thresholds for the volume of colour-coded changes defining a positive scan after examining the data. The primary US outcome was calcium deposits evidenced by linear hyperechoic deposits or bands in hyaline cartilage and/or hyperechoic sparkling spots in fibrocartilage or tendon [4]. The primary X-ray outcome was chondrocalcinosis, defined as calcific deposits in hyaline cartilage or fibrocartilage. For each imaging modality, location(s) of the primary outcome were recorded. Presence of the primary radiologic outcome at any location defined a positive scan.

We estimated sensitivity of each imaging modality using the uniformly minimum-variance unbiased estimate, equal to the percentage of subjects with a positive scan in the aspirated joint. We used the exact test to calculate 95% CIs. We calculated prevalence of positive scans in the standardized joint, rather than sensitivity, because a reference standard did not exist. DECT sensitivity and prevalence were calculated using two volume thresholds.

Ten of 27 eligible patients were enrolled. Mean (S.D.) age was 73.0 (9.7) years and 40% were female (supplementary Table S1, available at *Rheumatology* online). Acute

CPP crystal arthritis occurred in the knee in eight subjects and in the wrist in two subjects. Mean interval between arthrocentesis and enrolment was 16.9 (8.7) days. Sixty percent of subjects had received an IA CS injection.

Location of radiologic outcomes in the aspirated joint and volume of colour-coded changes on DECT are presented in Table 1; data for the standardized joint are in supplementary Table S2, available at *Rheumatology* online. In the aspirated joint, the minimum volume of colour-coded changes was 0.02 cm^3; 9 of 10 had a colour-coded volume >0.40 cm^3. Based on these data, we chose a lower threshold (>0.01 cm^3) that defined all aspirated joints as positive, and a higher threshold (>0.40 cm^3) that defined most but not all aspirated joints as positive.

In the knee, DECT colour-coded changes in the both the medial and lateral menisci were present in 8/8 knees (Table 1 and supplementary Fig. S1, available at *Rheumatology* online). US calcific deposits were observed in 8/8 knees; the meniscus had deposits in 4/8. X-ray chondrocalcinosis of the meniscus was present in 6/8. In the two aspirated wrists, DECT colour-coded changes were present in the intercarpal joints and triangular fibrocartilage complex but not the radiocarpal joint (i.e. aspiration site). In the standardized joint (wrist), DECT colour-coded changes were most frequent in the intercarpal joints (7/10) (supplementary Table S2, available at *Rheumatology* online). Calcification on conventional CT and colour-coded changes on DECT were strongly correlated in the knee and wrist, with the exception of the radiocarpal joint and first CMC joint (Cohen's kappa ~0.4) (supplementary Table S3, available at *Rheumatology* online).

In the aspirated joint, DECT sensitivity was 90% (62–100%) for volume >0.40 cm^3 and 100% (74–100%) for volume >0.01 cm^3. US sensitivity was 100% (74–100%) and X-ray sensitivity was 70% (42–91%). In the standardized joint, DECT was positive in 20% (4–49%) of joints using a volume threshold >0.40 cm^3; 90% (62–100%) had a positive DECT with a threshold >0.01 cm^3. US was positive in 80% (51–96%) and X-ray chondrocalcinosis was present in 30% (9–59%) of standardized joints.

This study adds to a small but growing body of literature on DECT sensitivity for CPPD *in vivo*. Tanikawa *et al.* reported the performance of DECT *ex vivo* using surgically excised menisci from 25 patients with severe OA [6]. DECT sensitivity was 77.8% (7/9) and specificity was 93.8% (15/16) using synovial fluid CPP crystals as the reference standard. Pascart *et al.* recently demonstrated that DECT distinguishes CPP deposits from hydroxyapatite *in vivo* [8].

We identified higher sensitivity of X-ray chondrocalcinosis for acute CPP crystal arthritis than two small studies in CPPD [6, 9]; US sensitivity was similar to prior reports [5]. DECT, US and X-ray comprise different fields of view, hence their sensitivities may not be directly comparable. Differences in meniscus visualization might explain why CPP deposits were noted in the meniscus in 8/8 knees on DECT, but only 6/8 on X-ray and 4/8 on US.

Limitations to this pilot study include small sample size and the lack of a control group. We required acute CPP crystal arthritis in case crystal location (synovial fluid *vs* cartilage) impacted results. It is possible that DECT sensitivity differs across CPPD subtypes; in gout, DECT was less sensitive in new-onset acute gout and non-tophaceous gout than tophaceous gout (supplementary material, section Additional references related to DECT in gout, available at *Rheumatology* online). Removing CPP crystals during aspiration might affect results, although arthrocentesis before DECT did not impact results in gout. Six subjects received an IA CS injection before enrolment; gout studies have not commented on whether this impacts DECT. DECT sensitivity changed slightly when different volume thresholds were used to define a positive scan; in gout, a DECT scoring system provided greater discrimination than volume of colour-coded changes. Given the small number of aspirated wrists, we were unable to consider joint-specific volume thresholds. Use of a 12 MHz US probe may have limited our ability to detect CPP deposits in superficial structures such as tendons.

DECT scanning is becoming increasingly widespread and has proven useful in gout. Future work with a larger sample and controls with mimicking conditions (e.g. gout, OA) will be critical to determine the sensitivity, specificity, positive and negative predictive value of DECT in CPPD. Establishing a scoring system to define a positive DECT and evaluating DECT performance in other CPPD subtypes will be of paramount interest.

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Sara K. Tedeschi[1], Daniel H. Solomon[1], Kazuki Yoshida[1], Kathleen Vanni[1], Dong Hyun Suh[1] and Stacy E. Smith[2,3]

[1]*Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital,* [2]*Department of Radiology, Division of Musculoskeletal Imaging, Brigham and Women's Hospital and* [3]*Neil and Elise Wallace STRATUS Center for Medical Simulation, Brigham and Women's Hospital, Boston, MA, USA*

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Correspondence to: Sara K. Tedeschi, Brigham and Women's Hospital, Division of Rheumatology, Immunology and Allergy, 60 Fenwood Road, Suite 6016, Boston, MA 02115, USA.
E-mail: stedeschi1@bwh.harvard.edu

Supplementary data

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Successful hydroxychloroquine treatment for familial Mediterranean fever in a Japanese patient with concurrent systemic lupus erythematosus

Rheumatology key message

- Hydroxychloroquine can be a novel therapy for patients with colchicine-resistant or colchicine-intolerant familial Mediterranean fever.

Sir, FMF is an inherited auto-inflammatory disease caused by mutations in the Mediterranean fever gene (*MEFV*) and characterized by recurrent and self-limiting acute fever attacks in a short period. SLE is a systemic autoimmune disease characterized by chronic inflammation and antibody production against elements of the cell nucleus [1]. HCQ, which is used for the initial treatment of SLE, has an inhibitory effect on the Toll-like receptor (TLR)-mediated activation of the innate immune response [2]. Although colchicine is an effective and safe drug in most patients with FMF, some patients cannot tolerate colchicine at an effective dose owing to side effects. Here, we report a rare case of a Japanese patient with concurrent FMF and SLE whose fever attacks associated with FMF showed a good response to HCQ.

In June 2010, a 31-year-old Japanese woman with a family history of recurrent fever attacks in her daughter was admitted to our department because of recurrent fever attacks, with high C-reactive protein levels, lasting for 1–3 days every 1–2 months since the age of 28 years. Although anti-nuclear antibody showed an increase of 160-fold (homogeneous), other immunological and serological results were negative. Genetic analyses for *MEFV* performed via direct sequencing revealed heterozygous E148Q and R202Q variants in exon 2 of *MEFV*. Additionally, genetic analyses for *MVK*, *TNFRSF1A*, *NLRP3*, *PSTPIP1*, *NLRP12*, *TNFAIP3*, *IL1RN*, *IL36RN* and *CARD14* performed via targeted next-generation sequencing revealed no other pathogenetic variants or mutations. Because recurrent fever attacks with arthritis gradually became more frequent, the patient was administered colchicine (1.0 mg/day), and her symptoms completely resolved for 6 months. The patient was eventually diagnosed with FMF. However, colchicine was discontinued because of gastrointestinal side effects. Thereafter, in October 2011, she newly presented with chronic arthralgia, facial erythema and oral ulcers. Laboratory findings initially showed lymphocytopenia (lymphocyte count 1130/μl) and later showed a low serum complement level (C4 11.7 mg/dl). Therefore, the patient was diagnosed with SLE according to the American College of Rheumatology 1997 revised criteria. Her chronic symptoms and laboratory abnormalities disappeared after prednisolone (15 mg/day) administration with tapering, followed by azathioprine (100 mg/day). However, the patient continued to experience recurrent fever attacks associated with FMF. She was re-administered colchicine (only 0.5 mg/day) considering the gastrointestinal side effects; however, the attacks did not completely resolve. In June 2017, she was administered HCQ (300 mg/day), following which she has not experienced recurrent fever attacks, and her remission has been maintained for 24 months. Additionally, the inflammatory cytokine levels (e.g. IL-1β, -6, -17, -12p40 and -12p70; IFN-α2 and -γ; and TNF-α) of peripheral blood mononuclear cells in culture supernatants showed an improvement after oral HCQ administration (Fig. 1).

The coexistence of FMF and SLE has rarely been reported [3]. Patients with FMF from Japan have a lower proportion of *MEFV* exon 10 mutations with high penetrance and a higher proportion of *MEFV* exon 2 variants with low penetrance compared with the findings in patients from Western countries and exhibit frequent atypical clinical symptoms, late onset and coexistence with autoimmune diseases [4]. On the other hand, although