Ultrasound imaging in crystal arthropathies: a pictorial review

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SUMMARY

Objective. The prevalence of crystal arthropathies in the general population is rising. The purpose of this pictorial study is to describe the sonographic elements of the most prevalent crystal arthropathies by emphasizing particular sonographic findings using illustrative images and cases while considering technical details and common pitfalls.

Methods. Using established recommendations, specialists in the fields of sonography and crystal arthropathies agreed by consensus on the unique ultrasound signs associated with each of the conditions.

Results. Gout, calcium pyrophosphate deposition arthropathy, and hydroxyapatite arthropathy are the three most prevalent crystal arthropathies. Today's high-resolution sonography enables reliable evaluation of the underlying crystal deposits, post-inflammatory changes, and a precise description of joint inflammation.

Conclusions. High-prevalence crystal arthropathies are reliably detectable by ultrasound with current ultrasound equipment. It is necessary to have extensive ultrasound training, know specific sonographic findings, and understand all possible differential diagnoses for disorders affecting the musculoskeletal system.

Key words: *CPPD, gout, ultrasound, hydroxyapatite, arthritis.*

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INTRODUCTION

In clinical practice, we frequently encounter crystal arthropathies in the management of patients with musculoskeletal disorders. The most common crystal arthropathies are gout (urate arthropathy), calcium pyrophosphate deposition arthropathy (CPPD), and hydroxyapatite arthropathy.

Modern high-resolution, multiplanar, and dynamic ultrasound imaging can be considered a well-established tool for the diagnosis and treatment (*e.g.*, ultrasound-guided injection, sonographic monitoring of response to drug therapy) of crystal arthropathies (1). Ultrasound imaging is a non-invasive examination that rapidly detects crystal deposits in various anatomic areas (*Supplementary Table 1*) with high sensitivity; moreover, it guarantees the detection of crystals at a "sono-histological" resolution (*i.e.*, 0.1 mm). The diagnostic potential of ultrasonography strongly depends on the experience of the examiner, the quality of the (high-end) equipment, and the high-resolution matrix probes used. Extended definitions for crystal deposition have been published and validated by the Outcomes Measures in Rheumatology (OMERACT) (2-4). The main findings of crystal deposition in joints are grouped in *Supplementary Table 1*. In this pictorial essay, we present sonographic aspects of crystal arthropathies using exemplary cases.

NON-SPECIFIC ULTRASOUND FINDINGS

Synovitis, bursitis, and tenosynovitis

Synovitis manifests on ultrasound as anechoic effusion (synovial fluid) or/and as isoechoic, hypoechoic (relative to subdermal fat), or more rarely hyperechoic synovial hyperproliferation, which may be visualized lying at the margin, appearing as villi, or as a synovial plica (*Supplementary*

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Figure 1). According to new definitions and grading of elementary components of synovitis, grey scale synovitis is hypoechoic synovial hypertrophy regardless of the presence of effusion and any grade of Doppler signal (5, 6). Synovial hypertrophy is defined as intra-articular or tenosynovial tissue that is not displaceable and poorly compressible and may show a Doppler signal in the presence of active inflammation. The Swiss Sonography Group in Arthritis and Rheumatism developed a semiquantitative synovitis score for exclusive use in patients with rheumatoid arthritis as early as 2007 (7). The composite (*i.e.*, composite B-mode and Doppler-mode score) semiquantitative synovitis score can also be used, for example, as a monitoring tool for crystal arthropathies, knowing that the scoring instrument has not yet been validated for this indication (8) (*Supplementary Table 2*). Not only in connective tissue disease, rheumatoid arthritis, or spondyloarthritis but also in CPPD, we typically see tendinosis and tenosynovitis. In CPPD and gout, for example, all flexor or extensor tendons may be affected in the hand. For crystal arthropathies, deposition of calcium in entheses, within tendons, or in ligaments is typical (Figure 1). In gout and CPPD, these deposits can occur anywhere; in gout (*Supplementary Figures 2 and 3*), they are common in the lower extremities (8).

Doppler

Doppler or B-flow signals can be detected within synovial or tenosynovial proliferations. We see increased or pathological vascularization by color Doppler, power Doppler, or B-flow within the synovial thickening due to neoangiogenesis, hypervascularization, or hyperperfusion in case of active inflammation (*Supplementary Figure 4*). An essential precondition for correct Doppler

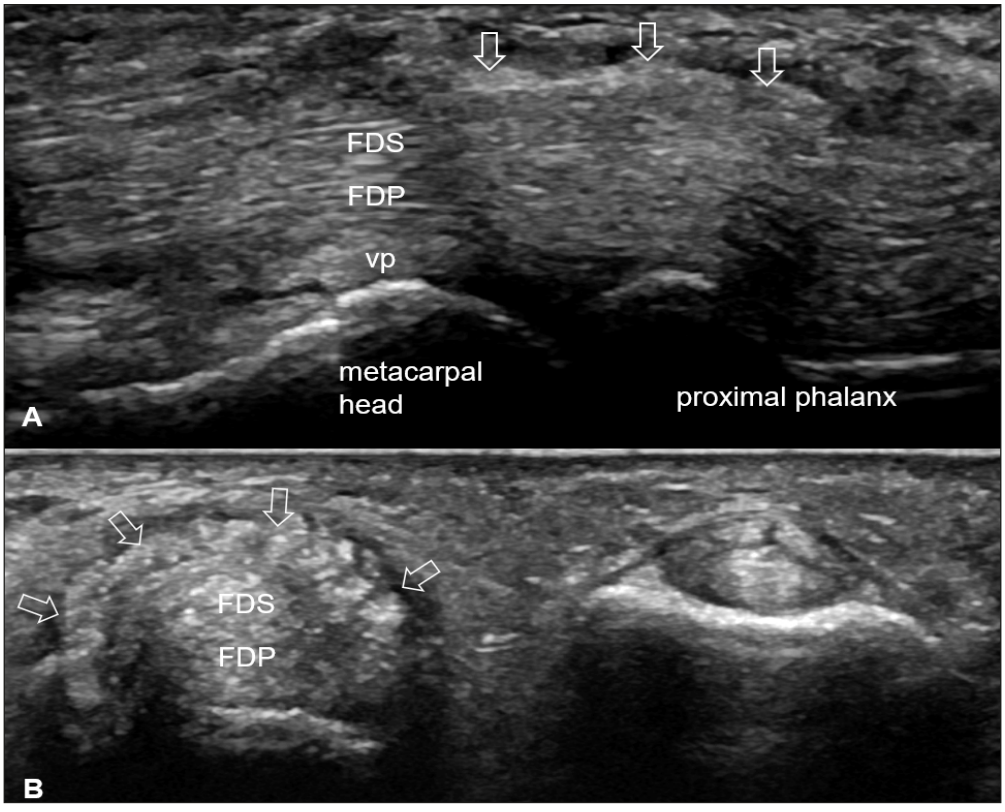

Figure 1 - Metacarpophalangeal joint palmar longitudinal (A) and transverse (B), B-mode, showing calcium pyrophosphate deposition (void arrows) within the A1 annular ligament. FDS, tendon of the flexor digitorum superficialis muscle; FDP, tendon of the flexor digitorum profundus muscle; vp, volar plate.

application is adequate adjustment of the device and careful examination of the joint (9, 10). The color always has priority over the B-mode (color priority). For power Doppler, the pulse repetition frequency is set as low as possible, usually between 500 and 750 MHz, so that artifacts are suppressed while the device remains set as sensitive as possible. The wall filter is set as low as possible. This is coupled to the pulse repetition frequency setting. The gain should be as close as possible to the threshold of noise appearance (6). The focus is where the highest sensitivity is required. With modern high-end equipment, this setting is unnecessary since the focus is automatically optimized throughout the image. Finally, set the Doppler window as large as necessary and as small as possible to focus on the region of interest. We recommend that ultrasound examinations focusing on synovitis be performed in the morning, not immediately after exposure to the cold, not after smoking, and not under high-dose non-steroidal anti-inflammatory drugs or steroids (11).

Example of synovitis in the wrist

The different synovial compartments of the affected joint (*e.g.*, in the wrist, the radiocarpal and ulnocarpal joints, the distal radioulnar joint, the midcarpal joints, and the carpometacarpal joints) are examined during a Doppler examination without probe pressure. A pannus-like synovial thickening may also occur around the ulnar styloid process. The origin may be, for example, the recessus sacciformis from the distal radioulnar joint (Figure 2) or tenosynovitis in the 5th (tendon of the extensor digiti minimi/quinti muscle) or more commonly in the 6th extensor tendon compartment (tendon of the extensor carpi ulnaris muscle). In a cohort of 91 patients with gout, hyperechogenic aggregates were found in the radiocarpal and midcarpal joints in 38.5% of cases (12). In a retrospective study, power Doppler signals were analyzed in inflammatory joint diseases such as gout, CPPD, rheumatoid arthritis, spondyloarthritis, and others and correlated with the number of cells in the synovial fluid analysis and with serologic markers of inflammation (13). Power Doppler hypervascularization was most pronounced in gout and calcium pyrophosphate deposits, although the average cell count in the synovium did not differ significantly between crystal-induced arthritis, rheumatoid arthritis, spondyloarthritis, and other inflammatory joint diseases. Power Doppler grades 0 and 1 were able to predict synovial leukocytes <5/nL and grades 2 and 3 predicted leukocytes ≥5/nL ($p<0.001$).

Erosions

Erosions are defined as intra-articular or extra-articular (especially in gout) disruptions of the cortical bone surface, which are shown in two planes (*Supplementary Figure 5*).

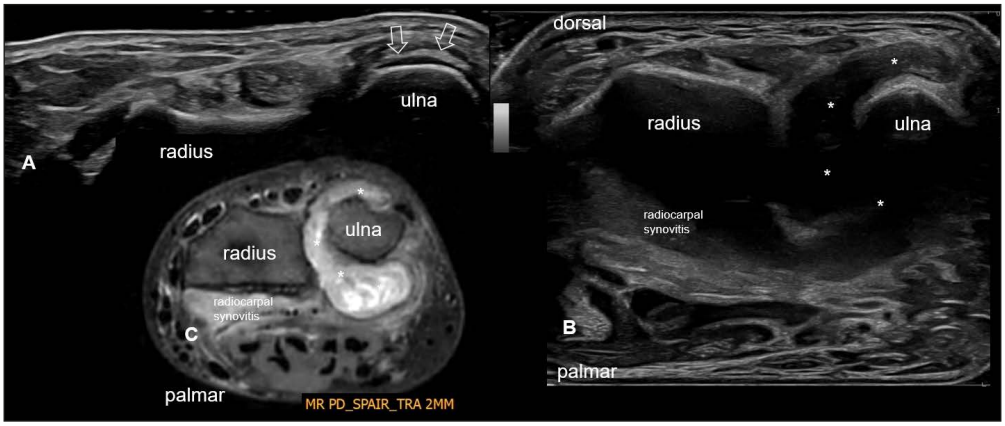

Figure 2 - Distal radioulnar joint in B-mode (A, B) and MRI image (C) showing ultrasound evidence of a "double contour" (void arrows) at the level of the ulna and synovitis in the recessus sacciformis (white asterisks).

Erosions may not only typically occur in rheumatoid arthritis; they may also be found in the more prevalent CPPD or in chronic non-tophous and tophous gout (14). A single small erosion is not necessarily pathologic and must be interpreted in the context of the clinical case. Normal bony defects crossed by the feeding vessels of the bone should always be differentiated from erosions (15). The OMERACT group is currently validating a semiquantitative erosion score taking into account the size and number of erosions and has already demonstrated that high-resolution ultrasound is a reliable tool for the evaluation and scoring of bone erosions, cartilage changes, and deformities in finger joints (8). High-resolution ultrasound allows early detection of erosive joint damage even in clinically unremarkable joints with higher sensitivity than radiography (16). Ultrasound is highly performant in detecting bone erosions depending on the site, with sites with a wider acoustic window presenting a greater advantage. Erosions in gout showed an association with the number of tophi present and not with their size (17). There was further association with age, duration of gout, synovial hypertrophy detected on ultrasound, and pathologic joint effusion.

Osteophytes

Osteophytes in secondary osteoarthritis in atypical joints such as metacarpophalangeal joints 2 (*Supplementary Figure 6*) and 3, wrists, elbows, or shoulders are common in CPPD and should also be specifically searched for. Compared to healthy individuals, gout patients have more bone erosions and even osteophytes (18). Multiplanar sonographic evaluation of osteophytes is simple and more sensitive than radiography, which corresponds to a summary view (19, 20). Ultrasound detected more osteophytes (53.2%) than radiograph (30.0%) and clinical examination (36.9%) in an exemplar osteoarthritis study (21).

■ ULTRASOUND FINDINGS IN CRYSTAL ARTHROPATHIES

In gout or CPPD, hyperechogenic structures can be visualized, for example, within the joint capsule, in the tendon sheath, in tendons themselves, at entheses, and within ligaments or the synovium.

Pitfall: the "snowstorm" sign refers to the appearance of floating, hyperechoic spots in the synovial fluid on ultrasound and is believed to have a high specificity for gout. Hyperechoic structures ("snowstorm" sign) within the anechoic fluid of a joint or tendon sheath are not specific for crystal arthritis (*Supplementary Figure 7*) (22). In healthy individuals, these dots correspond to physiologic gas bubbles within the viscous healthy synovial fluid (6). In addition, other etiologies are common in rheumatology practice that can cause a "snowstorm". Gas inclusions in septic synovitis, calcium pyrophosphate deposits, or, *e.g.*, fibrin accumulation/rice bodies in, *e.g.*, rheumatoid arthritis (22). At this point, we further emphasize that it would be better to avoid diagnosing crystal deposition only on synovial fluid ultrasound. In a study (2), ultrasound of synovial fluid was not reliable for identification of CPPD at the OMERACT exercises (mean κ 0.1) and has not been adequately tested in gout for reliability. In conclusion, nowadays, modern ultrasound does not yet allow reliable differentiation of the various crystals or gases within synovial fluids.

Calcium pyrophosphate deposition disease

Calcium pyrophosphate dihydrate, often known as CPP crystals, is a calcium salt that accumulates in cartilage and other articular tissues and causes a range of clinical symptoms. The chosen umbrella name for all discussions regarding CPP crystal deposition is CPPD. 3.4% of adult patients have CPPD-associated arthritis, making it the third most frequent cause of inflammatory arthritis. In daily life and reality, the condition affects a large portion of the population, particularly the elderly. However, it can manifest itself in a variety of ways. Any acute or chronic mono-, oligo-, or polyarticular inflammatory or non-inflammatory arthritis affecting people over the age of 55 should take this into account when making a diagnosis. Familial forms, certain metabolic illnesses (hyperparathyroidism, hemochromatosis, hypomagnesemia, dialy-

sis-dependent renal failure, *etc*.), and/or a history of joint trauma/meniscectomy need to be taken into consideration if they affect a patient under the age of 55. In CPPD, hyperechogenic calcifications are typically present within the hyaline cartilage or the fibrocartilage. Within the cartilage, both single-dot and linear hyperechoic calcifications can be visualized using high-resolution ultrasound probes (23) (Figure 3). Search for hyperechoic calcifications within the fibrocartilage typical of CPPD, *e.g*., in the triangular fibrocartilage complex [(TFCC) discus triangularis ulnocarpal)] (*Supplementary Figure 8*) or in a meniscus (24). In a cohort of 42 patients with a definitive diagnosis of CPPD, at least one TFCC component was found calcified in 37 (88.1%) patients. Hyperechoic calcifications (calcium salt, calcium pyrophosphate dihydrate [$Ca_2P_2O_7 \cdot H_2O$]) also occur within synovitis, *e.g*., in degenerative scapho-trapezio-trapezoidal osteoarthritis ("volcanic signs") (*Supplementary Figure 9*) (25). Occasionally, crystal deposits overlying the cartilage, as in gout, *i.e*., the "sandwich" sign with hyperechoic lines within and over the hyaline cartilage (*Supplementary Figure 10*). In trained hands, ultrasonography is at least as accurate, or more accurate, for the diagnosis of CPPD as synovial joint fluid analysis (26, 27). Clinically and sonographically, we distinguish different calcium pyrophosphate deposition arthropathies (CPPD as an umbrella term): for example, there may be asymptomatic chondrocalcionosis (demonstrated by imaging or histologic studies), acute calcium pyrophosphate arthritis, primary osteoarthritis (with secondary CPPD), or chronic CPPD with secondary osteoarthritis and recurrent arthritides (28). Approximately 5% of patients develop non-erosive, inflammatory seronegative" polyarthritis, which can mimic rheumatoid arthritis. In addition, CPPD is also found secondary to cartilage damage in the disease course of rheumatoid arthritis, typically after surgical orthopedic procedures (*e.g*., after knee arthroscopy), primary osteoarthritis, or in prolonged peripheral spondyloarthritides with structural damage, particularly to the hyaline cartilage. A recent systematic literature review and meta-analysis evaluated and compared the diagnostic accuracy of radiography and ultrasound (29). This showed excellent diagnostic accuracy for radiography [area under the curve (AUC)=0.889] and excellent diagnostic accuracy for ultrasound (AUC=0.954) considering synovial fluid analysis and histology (*Supplementary Figure 11*) as reference, gold standard (*Supplementary Table 3*).

Gout

In gout, we typically find hyperechogenic irregular crystal deposits overlying the hyaline cartilage ("double contour") in the chondrosynovial interface (*Supplementary Figure 12* and *Figure 4*) irrespective of the angle of in-

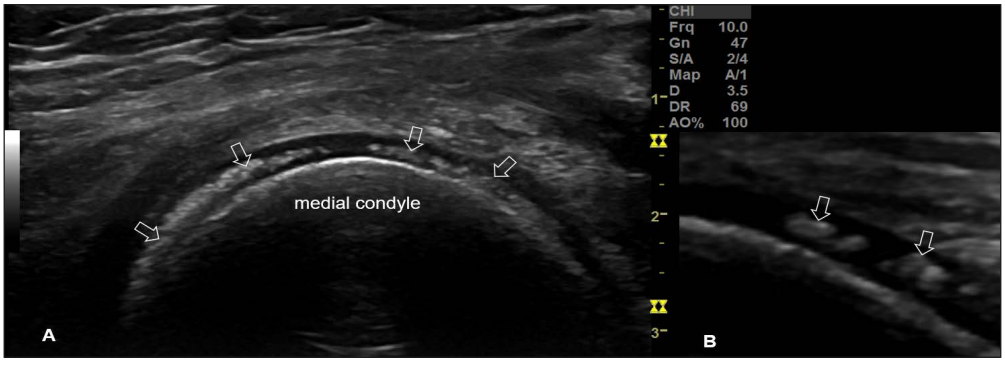

Figure 3 - Posterior knee, femoral condyle longitudinal, B-mode. A) Identification of hyperechoic linear and dotted calcifications (void arrows) within the anechoic hyaline cartilage in calcium pyrophosphate deposition arthropathy. B) Zoomed view with deep gain with continuing good visualization of calcifications in hyaline cartilage.

cidence of the ultrasound. Occasionally, this also occurs in CPPD: "sandwich sign" (*Supplementary Figure 10*). Gout and calcium pyrophosphate deposition disease can be distinguished from one another using dynamic assessment of the double contour sign: in gout, the double contour sign typically moves in synchrony with the subchondral bone, while in CPPD the movement occurs in the opposite direction (pseudo double contour sign) (30). This can be explained, among other things, by the fact that in gout, the crystals typically lie on the cartilage and move with the cartilage, whereas, in CPPD, the calcifications lie in the synovial membrane and, for example, in the joint capsule and ligaments (31). However, this does not always present a specific "double contour" (sensitivity of 43.7% and specificity of 99%) and shows a similar echogenicity as the respective underlying hyperechoic cortical bone. This "double contour" must be distinguished from a physiological interface sign (*Supplementary Figure 13*) between hyaline cartilage, and, *e.g.*, anechoic overlying fluid or overlying soft tissue (32). During a dynamic examination, the double contour on the cartilage moves with it, whereas the interface signs, which are to be regarded as normal, change their position depending on the angle of insonation. Think about false-positive double contour signs caused by thin cartilage, a joint effusion with an interface sign, or a normal hyperechoic appearance of the synovium. A false-negative double contour sign should also be taken into account since it could be caused by poorly seen joints with thin or damaged cartilage. Urate deposits may further appear as hyperechogenic smaller aggregates or as larger tophi. Tophi are sonographically iso- to hypoechoic masses without (soft tophi) or with possible partial or complete acoustic reflection (hard tophi), which may occasionally show a hyperechoic rim (33). Evaluation of one joint (radiocarpal joint) and two tendons (patellar tendon and triceps tendon) for hyperechogenic aggregates and three articular cartilages for the presence of a "double contour" provided the best sensitivity (85%) and specificity (83%) for the diagnosis of gout in a study by Naredo et al. (8). Hyperechoic deposits may appear similar to CPPD in gout, especially in the lower extremities, frequently at entheses (34). In asymptomatic patients with hyperuricemia but without manifest gout, clear subclinical urate deposits can be visualized (35). In 26 asymptomatic subjects with hyperuricemia over 2 years, a study on ultrasonography of the knee joints and first metatarsophalangeal joints showed urate deposits in 42% of patients, and after ultrasound-guided aspiration, urate deposits were confirmed at synovial fluid analysis in 82% of cases. Sonography is well established for objective and reproducible monitoring of therapy; the double contour sign and the tophus show statistically significant decreases during urate-lowering therapy, even after 3 months of treatment. Ultrasound is a promising tool for monitoring urate crystal deposition in patients during urate-lowering therapy in clinical trials and practice (36, 37).
Pitfall: different crystal arthropathies can be present at the same time (*Supplementary Figure 14*) (38).

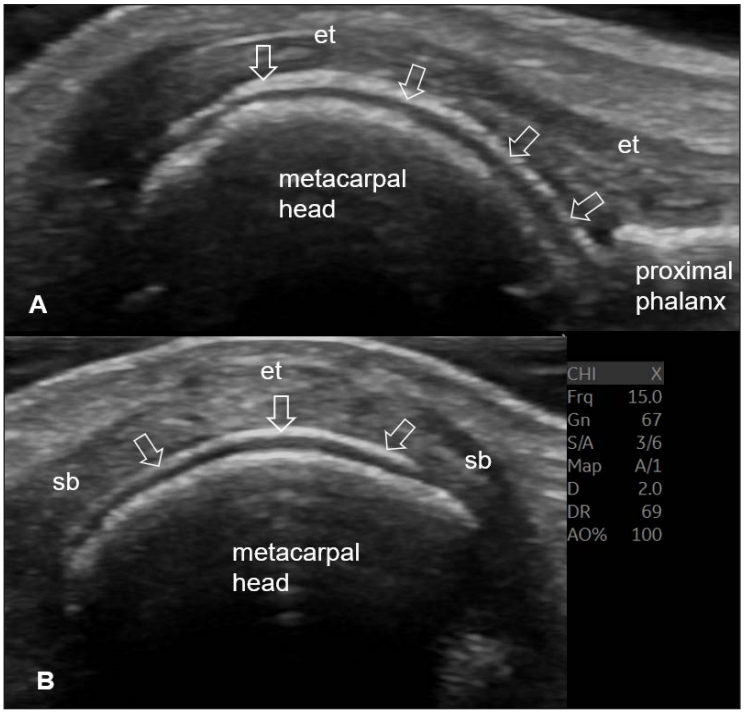

Figure 4 - Metacarpophalangeal joint dorsal longitudinal (A) and transverse (B) B-mode. Hyperechoic double contour in tophaceous gout, subcutaneous tophi visible in the clinical image (white asterisks). et, extensor tendon; sb, sagittal band.

Hydroxyapatite arthropathy

Calcifications within the joint capsule (in large joints as destructive arthropathy type "Milwaukee shoulder") or periarticular hyperechoic calcifications in the tendons (analogous to "calcifying" periarthritis), tendon attachments or ligaments also occur in hydroxyapatite arthropathies. Hydroxyapatite deposits can lead to acoustic reflection, depending on the density of the calcium deposit, which in turn leads to the fact that we no longer find an acoustic signal far from the source of the ultrasound (34). Identification of basic calcium phosphate crystals in synovial fluid is difficult and requires special alizarin red staining (*Supplementary Figure 13*), which is not standard and is ordered separately (39, 40). On the other hand, for example, hydroxyapatite deposits are frequently found in joint capsules in finger osteoarthritis. Intra- and periarticular basic calcium phosphates are found in over 60% of patients with osteoarthritis in general. Calcium deposits are also found in the tendons or tendon sheaths of the hand and can lead to acute inflammation ("Philadelphia finger") (41). The basic calcifications can be hard with consecutive complete acoustic reflection ("acoustic cancellation with acoustic shadow"); they can further appear fragmented, nodular-soft, or cystic with a hard edge and a softer core (Figure 5) (42). Hydroxyapatite calcifications occasionally show a "twinkling artifact" in the Doppler examination. These twinkling artifacts can occur on rough, highly reflective surfaces (color Doppler signals in all colors), *e.g.*, behind calcifications, kidney stones or air, which can lead to improved detection, especially in deeper tissue layers. Pitfall: whether a calcification reflects or absorbs ultrasound signals or whether acoustic attenuation is present depends, among other things, on the crystal concentration and the size of the deposit. This could also be shown in a radiographic and sonographic study with examinations of synthetic crystal suspensions with increasing concentrations of crystals for all three crystals mentioned above (42). In this model, the synthetic calcium pyrophosphate suspensions did not result in complete acoustic reflection with "acoustic canceling" ("acoustic shadowing") away from the source, whereas this was shown with increasing concentrations for both urate crystals (>420 mg/mL) and hydroxyapathite crystals (>153 mg/dL). The authors of this in vitro study highlight the potential ability of ultrasound to discriminate between the 3 crystals based on their appearance and variable attenuation of ultrasound signals in the B-scan (*Supplementary Figure 15*).

Contributions

GT, original concept of study and writing of the manuscript; TH, VR, GF, critical review of the manuscript.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations that might negatively affect the contents of this publication and/or claim authorship rights to this publication.

Ethics approval and consent to participate

No ethical committee approval was required.

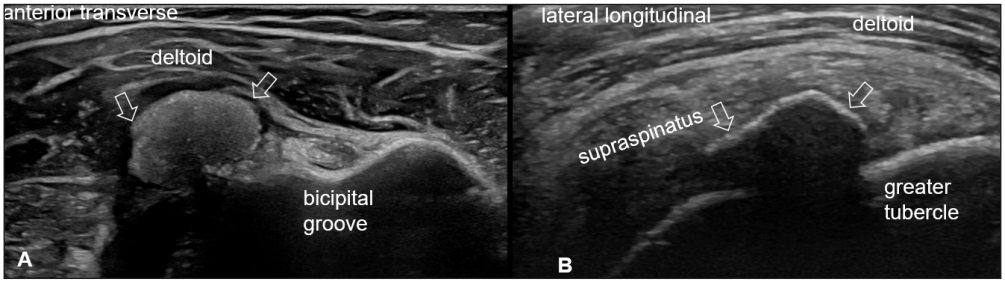

Figure 5 - Anterior shoulder transverse (A) and lateral shoulder longitudinal (B), B-mode, showing evidence of soft (arrows above) and hard calcification in calcific tendinitis due to hydroxyapatite deposits.

Patient consent for publication
Patients gave written, informed consent for the use of the published images according to the principles issued by the World Medical Association – the Declaration of Helsinki.

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Availability of data and materials
Data and materials are available from the corresponding author upon request.

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Supplementary material available online