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Invited Review

Usefulness of ultrasound in the diagnosis of crystal deposition diseases

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Abstract

Gout and calcium pyrophosphate crystal deposition disease (CPPD) are common forms of inflammatory arthritis whose prevalence has increased in recent years. Although the identification of monosodium urate crystals (MSU) and calcium pyrophosphate crystals (CPP) in synovial fluid (SF) by polarized light microscopy are the gold standard for diagnosing these diseases, SF analysis is not always available. An early diagnosis and specific treatment, especially in gout, allows avoiding irreversible structural damage, comorbidities, and a severe impact on the quality of life of patients. Musculoskeletal ultrasound (US) is a noninvasive tool that allows detecting aggregates of microcrystals at multiple anatomical sites and helps to establish a specific diagnosis. The objective of this review is to evaluate the applications of US in the diagnosis and clinical management of the main microcrystalline arthropathies. The US has helped improve our understanding of the natural history of the disease, due to its ability to visualize not only soft tissue inflammation and structural damage, but also the characteristics of MSU and CPP crystal deposition. The anatomical sites of crystal deposition are also a key factor for differential diagnosis in different microcrystalline diseases. The US allows establishing an early diagnosis, especially in asymptomatic hyperuricemia, to discriminate with other inflammatory diseases, to assess the extent of microcrystalline deposition and their sensitivity to change after treatment. Given its increasing availability in clinical practice and strong evidence, US is a bedside imaging technique helping clinicians to improve diagnosis and therapy monitoring in their daily practice.

Keywords: Gout, calcium pyrophosphate crystals, chondrocalcinosis, imaging, ultrasound

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Introduction

US examination has proven to be an excellent technique for efficient and accurate evaluation of soft tissues in rheumatic diseases. Over the last few years, great advances in US equipment have been achieved, such as better image quality and higher Doppler sensitivity. These advances have contributed to improving the diagnosis of inflammatory diseases, monitoring disease activity, and response to therapy.

The aim of our review is to describe, discuss and evaluate the current level of knowledge of the US use in crystal deposition diseases diagnosis and clinical management.

Gout

Gout is one of the most common types of inflammatory arthritis. It is a painful and disabling disease that normally results from the interaction of genetic, constitutional, and environmental risk factors.

The prevalence of gout and/or hyperuricemia in the overall study population has increased over the past decade. However, the epidemiology of gout is difficult to quantify due to the usage of different methodologies among studies, such as case definition and the means of estimating incidence and prevalence. The prevalence of gout ranges from 0.9 to 2.5% in Europe, 3.9% in the USA, and over 6% in some Oceanic-Pacific ethnic groups.[1]

Its incidence is estimated to be approximately 1 or 2 per 1,000 person-years. It is more common among men and it is strongly age-related. Its prevalence increases with age to rates of up to 7% in men aged over 65 and 3% in women aged over 85. Gouty patients also have comorbidities such as renal and cardiovascular disease, and gout treatment may help reduce the incidence and severity of those comorbidities.

Gout is characterized by disturbances in purine metabolism and urate excretion, bringing about the deposition of monosodium urate (MSU) in synovial fluid (SF) and other tissues.

Unfortunately, gout is frequently misdiagnosed and underdiagnosed. The gold standard for the diagnosis of gout is the microscopic evaluation of the synovial fluid or tophi aspirate, which reveals the presence of negative birefringent MSU crystal under polarizing microscopy. Although joint aspiration is not a difficult procedure, its performance and subsequent evaluation of SF requires training and available technical tools.

The use of US is a noninvasive alternative approach to achieve diagnostic efficiency and precision in gout.

Imaging in the diagnosis of gout

Diagnosis of gout is mostly based on the clinic features and elevated serum urate levels. But often, without microscopic verification of MSU crystals, the diagnosis is delayed and the disease progresses to irreversible structural damage. For this reason, other means are often required to confirm the diagnosis of gout.

Conventional radiography (CR), magnetic resonance imaging (MRI), dual-energy computed tomography (DECT), and ultrasound are imaging tools that can assist in the diagnosis and management of gout. But perhaps each technique plays a role in the different stages of gout disease.

CR can document advanced manifestations of chronic gout, such as bone erosion, joint space narrowing, and tophi. In contrast to US and DECT, CR cannot detect synovitis and deposition of MSU, in the absence of clearly identifiable tophi. A particularly strong association was found between MSU crystalline deposits and joint erosion scores.[2]

Although MSU deposition cannot be directly visualized by MRI, this technique provides information about the size of tophi, synovitis, joint effusion, soft-tissue edema, and bone erosions. However, MRI findings are not specific from other forms of inflammatory arthritis and it is expensive and not always available.

Conventional computed tomography and especially DECT are techniques that, due to different absorption properties, discriminate MSU deposition from connective tissue and calcium-containing structures. DECT provides an accurate and direct measure of MSU deposition (detection and quantification of tophi) even in atypical locations. DECT has a sensitivity of 88% and specificity of 90% for diagnosing gout, but its sensitivity is lower in patients with recent onset of the disease.[2] However, DECT has limited access, and repeated images from multiple locations probably carry unacceptable radiation exposure.

Musculoskeletal US is an imaging tool characterized by a wide set of advantages including the lack of radiation, it is easily accessible, without any specific contraindication, low cost, adequate reproducibility data, well-accepted by the patient, and the possibility of dynamic, real-time scanning. In addition, it improves the effectiveness of targeted arthrocentesis by selecting SF puncture areas. Its main limitation is being a very operator-dependent technique.

Due to their physical properties, UMS crystals deposited in the joints reflect ultrasound waves more intensely compared with surrounding tissues, allowing easy visualization and making ultrasound an accurate detection technique.

The US has the potential to detect crystal deposition in different anatomical areas, even small amounts of MSU crystals deposited on articular cartilage in individuals with asymptomatic hyperuricemia. Therefore, the US can play an important role in improving the early diagnosis and treatment of gout by offering a therapeutic window of opportunity. It also allows a treat-to-target management of disease to achieve remission and avoid progressive structural damage.

Ogdie et al.[3] reported the results of a large, multicenter observational cross-sectional study providing evidence that US features of MSU crystal deposition had high specificity and high positive predictive value (PPV) with a limited sensitivity for early gout. Specificity remained high in subjects with early disease and without clinical signs of tophi. US can easily identify elementary gout lesions with high intraobserver reliability and moderate to low interobserver reliability.[4]

Only US and DECT could be useful to assess tophus resolution in response to ULT. Musculoskeletal US is a valid and reliable imaging tool for the diagnosis of gout and one of the cornerstones in early detection of crystal deposits, monitoring of treatment, and remission of the disease.

Ultrasound in the diagnosis of gout

Identification of MSU crystals is not always possible. This is due to the difficulty with articular aspiration in small joints, presence of a small amount of fluid, and deposition of extra-articular crystals. In cases of unproven gout with crystals in the joint aspirate, clinical, radiographic, and laboratory evaluation may be helpful in making the diagnosis. However, during an acute gout attack, serum uric acid levels may be within normal limits.

The GEMA-2 study[5] is the cross-sectional assessment of gout management by rheumatologists. The results of this study show that despite being the gold standard, the diagnosis rate of crystal-proven gout was only 32%. Furthermore, aspiration of synovial fluid may not reveal MSU crystals in up to 25% of gout patients. The presence of MSU crystals in SF or tophus aspirates has a 100% specificity in gout. However, the sensitivity is lower, in acute gout, it is 84%, and in intercritical gout it reaches 70%.[6] In addition, the presence of crystals of MSU in SF does not exclude other causes of concomitant arthritis such as septic arthritis or calcium pyrophosphate crystals (Table 1).

The ACR-EULAR Gout Classification Criteria published in 2015,[7] do not necessarily cover the full spectrum of the disease, essentially incorporating hyperuricemia, evidence of

Main Points

- US is a useful and noninvasive tool that can detect microcrystalline aggregates in multiple anatomical areas of patients with gout and calcium pyrophosphate deposition disease (CPPD).
- US has been shown to be a more sensitive technique for detecting CPPD than conventional radiology; It would be the first technique option used for the diagnosis of CPPD and gout.
- US can be used as a safe and reliable guide to aspirating even minimal fluid collections suitable for microscopic analysis.
- US is useful to diagnose early gout, even in the phase of asymptomatic hyperuricemia, allowing a window of therapeutic opportunity. It has also been shown to be useful in monitoring the dissolution of urate crystals and evaluating disease remission after treatment.
- Anatomical sites are a key factor for differential diagnosis in microcrystalline arthropathies. The first metatarsophalangeal and the knee in gout and the medial area of the knee and the triangular carpal fibrocartilage in CPPD are the locations with the highest diagnostic profitability.

Table 1. Meaning of the presence or absence of crystals in SF.

No crystal presence	Crystal presence
Gout is discarded?	MSU crystals negative birefringence: • Gout is confirmed
Technical problem: • Crystal dissolution because of a delay in processing the sample • No experience in crystal identification on polarizing microscopy	Other crystals negative birefringence: • Cholesterol crystals • Steroid crystals • Cartilage • Powder
• Ultramicroscopical crystals • Joint effusion next to crystal deposit area	Other forms of inflammatory arthritis: • Concurrent gout and CPPD • Septic arthritis

SF, synovial fluid; MSU, monosodium urate; CPPD, Calcium pyrophosphate deposition disease

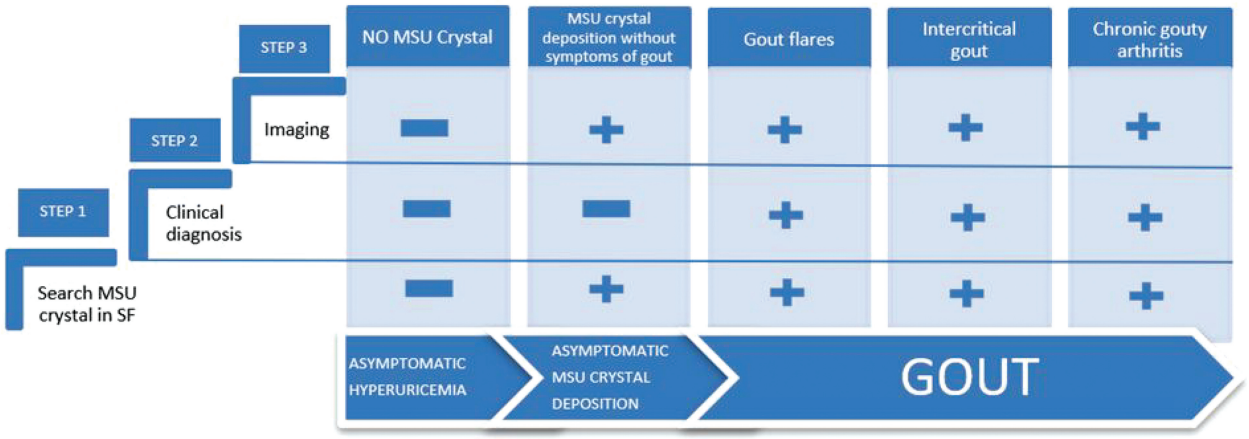


Figure 1. EULAR three-step approach for the diagnosis of gout.

crystallization, acute and/or chronic inflammation, and evidence of damage in the form of bone erosions. In these criteria, the presence of MSU crystals in SF is a sufficient criterion to classify the subject as gout. But there are other different domains that can help in the diagnosis of gout. The image domain includes double contour sign (DCS) on US, urate on DECT, or radiographic erosions. The presence of DCS can increase the score by 4 from a possible maximum of 23. A score > or equal to eight classifies as gout, with 89% sensitivity and 85% specificity. However, a major limitation of these criteria is that it only includes DCS and do not include other elementary gout lesions, such as tophi, with high specificity.

The 2018 updated EULAR recommendations for the diagnosis of gout[1] established eight recommendations, including the identification of MSU crystals in SF or tophus as the gold standard and a sufficient criterion for gout classification according to the 2015 ACR/EULAR criteria.

A three-step approach for the diagnosis of gout is recommended. First, identification of MSU crystal in SF. If it is not possible, the second step relies on clinical diagnosis based on clinical features of gout and the presence of hyperuricemia. When a clinical diagnosis of gout is uncertain and crystal identification is not possible, the third step recommends that patients should be investigated by imaging to search for MSU crystal deposition with US, DECT, conventional TC, or MRI (Figure 1).

The task force agreed that US can be more helpful in establishing a diagnosis in patients with gout flare or chronic gouty arthritis by detection of tophi or DCS, which is highly specific for urate deposits in joints.

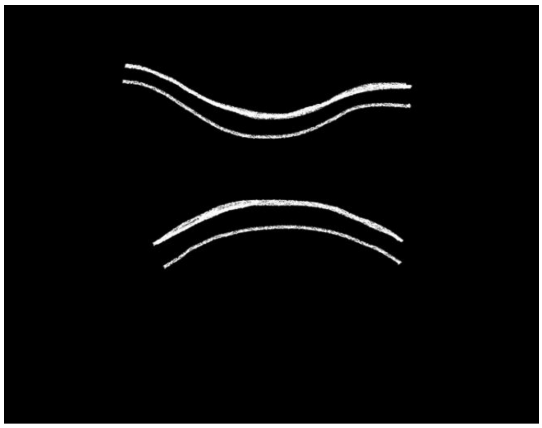
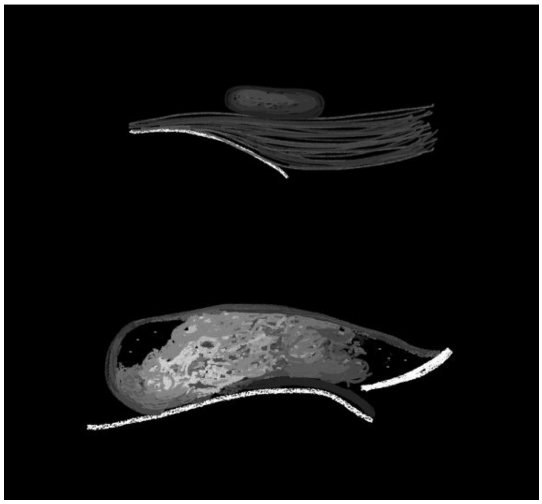
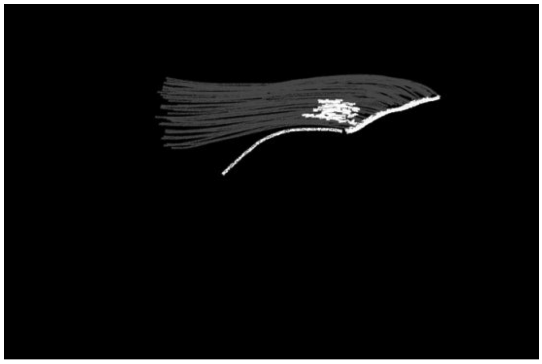
Ultrasound findings of gout: Elementary lesions

Double contour sign

According to the Outcome Measures in Rheumatology (OMERACT) Ultrasound Gout Task Force group in 2015 developed consensus definitions of US gout elementary lesions (Table 2).[8,9] The DCS is an abnormal hyperechoic band (due to urate crystals deposits) over the superficial margin of articular hyaline cartilage and distinguishable and thicker than the sign of the cartilage interface (Figure 2). This sonographic finding is consistent with histopathological studies that showed a particular predilection for the crystallization of uric acid on the surface of hyaline cartilage.[10] The most frequent DCS sites are the articular cartilage of metatarsal heads (Figure 3), metacarpal heads, femoral condyles, and humeral heads. Thiele and Schlesinger[11] demonstrated this US finding in 92% of gouty joints and in none of the controls. DCS is highly gout-specific, but is not present in all patients, ranging in sensitivity from 0.22 to 0.92, and moderate reliability was shown in OMERACT multicenter exercise results.

It can be differentiated from the calcium pyrophosphate (CPP) crystal deposits that are usually found within articular cartilage. The distribution of crystal deposits at the cartilage level is mainly related to the site of their formation: Synovial cells for urate crystals and hyaline cartilage for CPP crystals.[12] Löffler et al.[13] in their study suggest that concomitance of DCS, hypervascularization, and elevation of serum urates make the diagnosis of gout seven times more likely than that of CPP deposition disease or inflammatory

Table 2. US findings of gout: Elementary lesions.

US elementary lesion	OMERACT definition	Picture
1- Double contour sign	Abnormal hyperechoic band over the superficial margin of the articular hyaline cartilage, independent of the angle of insonation and which may be either irregular or regular, continuous or intermittent and can be distinguished from the cartilage interface sign	
2- Tophus	A circumscribed, inhomogeneous, hyperechoic and/or hypoechoic aggregation(which may or may not generate posterior acoustic shadow), which may be surrounded by a small anechoic rim	
3- Aggregates	Heterogeneous hyperechoic foci that maintain their high degree of reflectivity even when the gain setting is minimized or the isonation angle is changed, and which occasionally may generate posterior acoustic shadow	
4- Erosion	An intra-and/or extra-articular discontinuity of the bone surface (visible in two perpendicular planes)	

Own elaboration by Moragues et al.

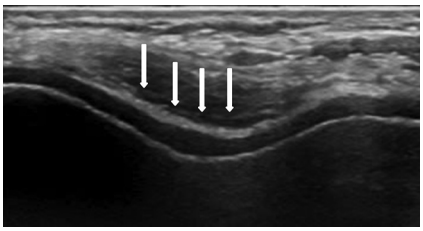


Figure 2. Double contour sign (DCS). Hyperechoic enhancement of the chondrosynovial interface secondary to the monosodium urate crystal deposition. Transversal scan of the femoral cartilage surface.

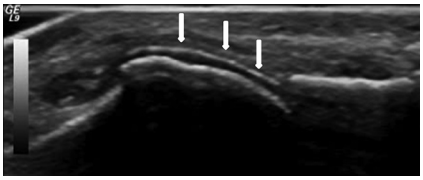


Figure 3. Double contour sign (DCS). Longitudinal view of the dorsal aspect at the first metatarsophalangeal joint in a gout patient.

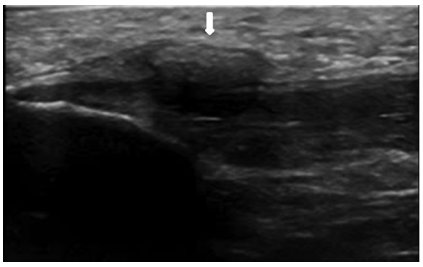


Figure 4. Tophus on proximal patellar tendon (arrow). Note the circumscribed, inhomogeneous, hyperechoic aggregation, without acoustic shadow.

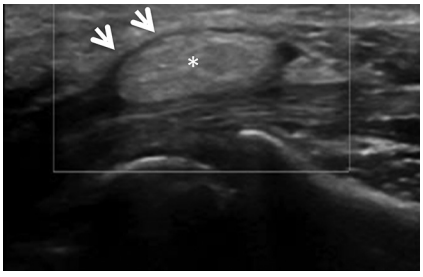


Figure 5. Tophus (*) in the wrist volar region on the flexor tendons, surrounded by an anechoic halo (arrows).

arthropathies. However, some patients may have concurrent diagnoses of gout and CPP disease.[13,14]

Tophus

Larger accumulations of MSU crystals develop tophus, which can be located extra-articular, intra-articular, or intratendinous (Figure 4).

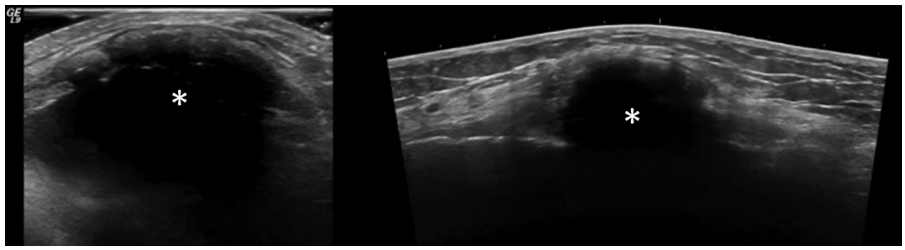


Figure 6. Tophus may generate posterior acoustic shadow (*) due to the crystal density of MSU crystals.

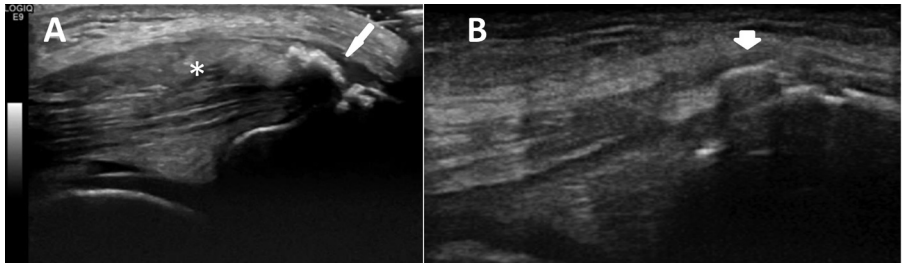


Figure 7. A, B. (A) Patient with gout. Longitudinal image of the quadriceps tendon enthesis. A tophus is observed on the tendon (*) and hyperechoic aggregates in its enthesis (arrow). (B) Other case of gout patient. The quadriceps tendon inserting into the patella in a longitudinal scan. The image showing loss of the typical fibrillar pattern, enthesophytes, and hyperechoic aggregates within the tendon (arrow).

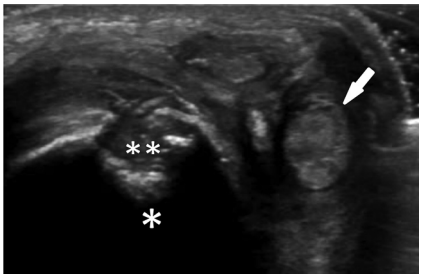


Figure 8. Bone erosion in a patient with gout (*) of extraarticular location and adjacent to intratendinous aggregates (**) in the triceps enthesis in the elbow. Several tophi and aggregates are seen inside the olecranon bursa (arrow).

Tophus is a circumscribed, heterogeneous, hyperechoic, and/or hypoechoic aggregation that[1] may be surrounded by a small anechoic rim (Figure 5), it may or may not generate posterior acoustic shadow (Figure 6). *In vitro*, tophi are surrounded by an inflammatory reaction, a rim of macrophages, lymphocytes, and large foreign body giant cells. This may explain US finding of anechoic rim surrounding tophi.[15] Tophi often have a characteristic sonographic appearance of "wet sugar clumps." This appearance reflects the histological composition of tophi, which is of MSU crystals together with fibrovascular tissue and inflammatory cells.[16]

The tophus lesion has high gout specificity of 0.8 (0.38-0.96), but a variable sensitivity among studies.[1]

The OMERACT reliability for tophus is good, it has the highest reliability of the four elementary lesions.

Aggregates

Deposits of crystals not large enough to be defined as a tophus were defined as intra-articular or intratendinous aggregates (Figure 7). Their role in the diagnosis of gout has not yet been determined. Since a tophus is also a collection of aggregates, there is a risk that these two elementary lesions overlap (Figure 8).

Erosion

The US definition of bone erosion in gout is the same as in rheumatoid arthritis. However, the location varies, in gout bone erosions are extra-articular and adjacent to tophaceous material (Figure 9).[17] Erosions visualized by ultrasound have a higher sensitivity than conventional radiography, even early gouty small erosions, so US evidence of structural damage is identified earlier (Figure 10). However conventional computed tomography and magnetic resonance are better in detecting erosions in gout patients.[18]

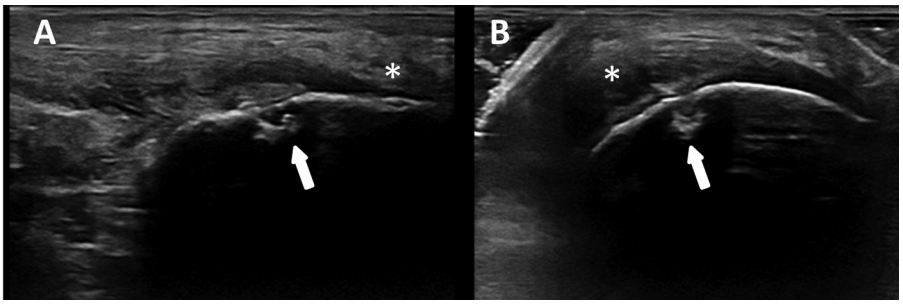


Figure 9. A, B. (A) Cortical erosion (arrow) in the calcaneus at the insertion of the Achilles tendon (longitudinal plane). (B) transverse plane). A tophus is observed related to the enthesis (*).

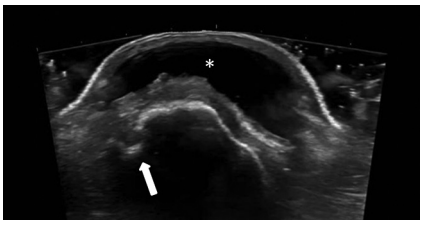


Figure 10. First episode of acute gouty arthritis in the first metatarsophalangeal joint with synovial effusion in the bursa (*). Metatarsal head already has an erosion in the bone cortex (arrow).

Other US findings

The snowstorm appearance has not been validated, but it has been described as hyperechoic dots (presumably urate crystal aggregates) swirling in the synovial fluid when the joint is agitated.[19]

US can demonstrate inflammation in gout, including joint effusion, synovial hypertrophy, Doppler signal, and soft tissue edema (Figure 11). The Doppler mode allows the detection of hyperemia in joints and tendons indicating active inflammation. These nonspecific ultrasound findings, such as synovitis and tenosynovitis, are not included as elementary lesions in gout. In these cases, the validated OMERACT definitions for rheumatoid arthritis must be applied.[17,20] There is no evidence that synovial hypertrophy in gout patients invades the subchondral bone as in rheumatoid arthritis.

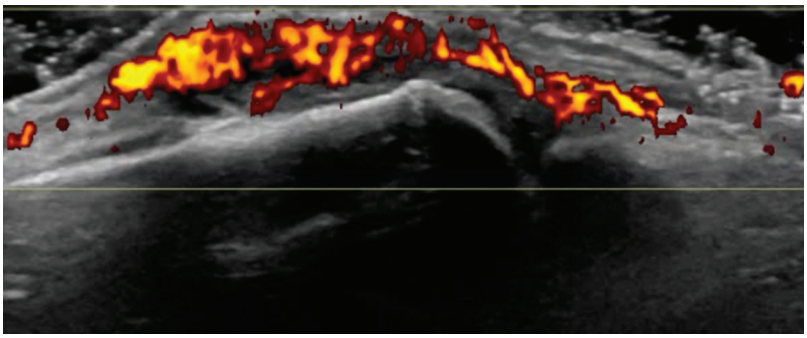


Figure 11. Synovitis with intense Doppler signal in an acute inflammatory episode of gout in second metacarpophalangeal joint.

The ability of ultrasound to detect inflammation is very useful in patients with intercritical gout without clinical inflammation and in those with a high burden of tophi and persistent chronic inflammation (Figure 12). These findings will be important for evaluating sensitivity to change with ULT or maintaining prophylaxis treatment to control persistent inflammation.

In patients with typical clinical signs and ultrasound findings such as DCS, tophi, and erosions, gouty arthritis can be diagnosed and treatment can be started without performing joint aspiration.

Ultrasound in asymptomatic hyperuricemia

Hyperuricemia is defined as an increase in serum MSU concentration. When the serum MSU concentration exceeds the solubility of urate (above 6.8 mg/dL), supersaturation of urate in the serum and other extracellular spaces results. However, the solubility of MSU decreases with the temperature, which may explain that gout chiefly involves distal joints that are colder than the central part of the body. At 35 °C—the estimated temperature of the great toe—MSU reaches its solubility limit at a concentration of 360 mol/L (6 mg/dL).

In general, crystallization of MSU occurs when the serum level exceeds its saturation point. However, nucleation and deposition of MSU crystals are very slow processes depending on multiple genetic and environmental factors, as well as the magnitude of the hyperuricemia, and its duration.[21]

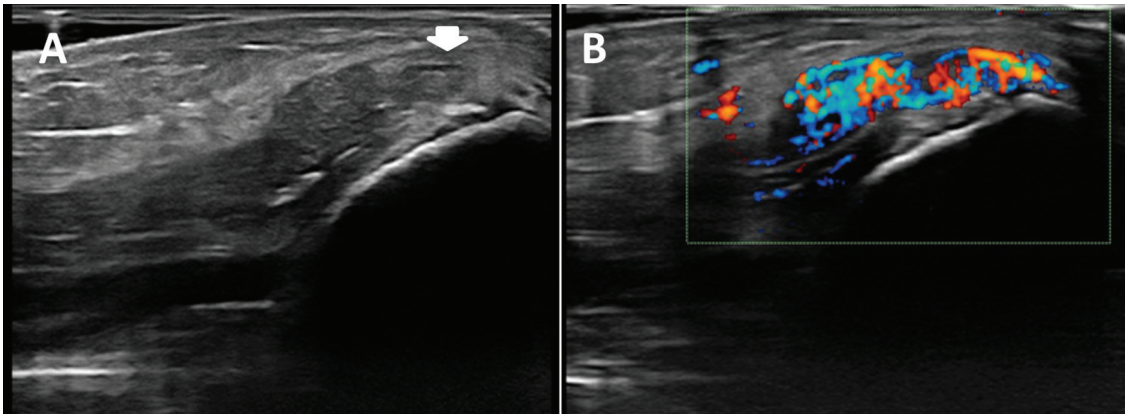


Figure 12. A, B. (A) Triceps tendon enthesis of the elbow with adjacent tophus in grayscale (arrow). (B) In the color Doppler image, an intense Doppler signal is observed in the tophus. The patient did not report symptoms in the elbow.

Although the incidence of gout increases with rising serum urate levels, and hyperuricemia is a strong predictor of incident gout. Many individuals with hyperuricemia remain completely asymptomatic, a condition referred to as asymptomatic hyperuricemia (AH).

AH is defined as a serum urate concentration equal to or above 7.0 mg/dL with no symptoms or clinical signs.

Deposition of urate crystal in joints starts much earlier than symptomatic gouty arthritis. High-resolution US recently gained interest in the assessment of gout due to its ability to visualize not only soft tissue inflammation and joint damage but also MSU crystal deposition.[9]

Despite a similar level of urate concentration throughout the body, MSU crystal deposition and gout-related features have a certain propensity for the first metatarsophalangeal (MTP1) joint. The reason is not clear, but it may be associated with biomechanical load or physical stress during gait, or the co-occurrence of MTP1 osteoarthritis.

De Miguel et al.[22] identified urate crystal deposition in 34.6% of individuals with HA with MSU crystals confirmed in SF. The preferred sites were the MTP1 joint (33.3%) and the knee (25%) and the most frequent ultrasound finding was DCS. Combination of knee and MTP1 joint sites had 45.8% prevalence of urate crystal deposition. A higher percentage of DCS in this study as compared to previous studies could be due to the screening of more sites. Two other studies have reported that a four-joint scan (both knees and first metatarsophalangeal joints) for aggregates and DCS sign is sufficient for the diagnosis of gout.[23,24]

Stewart et al.[25] conducted a systematic review to determine the prevalence and discrimination of OMERACT-defined elementary US lesions of gout in people with AH. They found that on people with AH, scanning of the MTP1 and femoral condyle for double DCS, plus the MTP1 for tophus, has the highest prevalence and discrimination compared to those with normo-uricemia.

The evidence of urate crystal deposition in articular cartilage by US has led to the description of the natural history of hyperuricemia and gout stages: Asymptomatic MSU crystal deposition during which people have MSU crystal deposition in the absence of gout; gout defined by MSU crystal deposition and clinical disease elements such as gout flare, chronic gouty arthritis, and tophi.

In a study designed to identify US features of the MTP1 joint in people with gout and people with AH compared with normo-uricemic controls, Stewart et al.[26] found that individuals with AH do not demonstrate features of inflammation or bone erosion on US. However, they did display a similar frequency of urate deposition at the MTP1 joint that people with gout.

Utility in treatment monitoring

At present, there is a consensus that in cases of symptomatic hyperuricemia (gout, urate-nephrolithiasis), a urate-lowering therapy (ULT) should be started, urine alkalization considered and, when possible, drugs inducing hyperuricemia discontinued.

The initiation of ULT and follow-up in cases of AH should consider urinary sediment analysis, musculoskeletal US, renal function, and serum urate levels.[27] It is reasonable to start ULT in patients with urate precipitates in urine (recognized in the sediment) and in joints (recognized by US).

Some studies in patients with prolonged AH $\geq$ 2 years confirmed that 34-42% show MSU deposits and 24% evident inflammation (Doppler signal), so all patients with long-standing AH should get an US (knees and metatarsophalangeal), because the US findings and its subsequent treatment could modify the clinical course of "asymptomatic hyperuricemia," challenging the current standards described in European and American guidelines.[28]

Given its increasing availability in clinical practice, ultrasonography has the potential to be useful in disease monitoring. Since both tophus and DCS are specific to gout, these two features appear particularly relevant to assess.[9]

Small studies have shown that lowering serum MSU levels can lead to the disappearance of DCS. Thiele et al.[29] reported in five patients a good correlation between low MSU levels and disappearance of DCS, they were treated with urate-lowering agents who had maintained MSU levels below 6 mg/dL for at least 7 months.

Few studies have also demonstrated that ultrasonographic measurements of tophi are sensitive to change in response to ULT. A prospective study[30] of patients with crystal-proven gout starting ULT demonstrated that index tophus volume and maximal diameter measured by ultrasonography changed over a 12-month period, with a strong relationship between urate concentrations and change in measured size. In connection with this, Ottaviani et al.[31] suggested that screening for specific features of gout such as tophi or DCS by US at the initiation of ULT and during follow-up is a sensitive way to detect the disappearance or decrease in urate deposits in gout. Moreover, the correlation was good between modification of US-observed features of gout and serum MSU levels decreased to below the recommended serum MSU objective.

The changes of Doppler signal during ULT were assessed by Peiteado et al.[32] They found that Doppler US findings showed significant improvement after ULT in gout patients, but its persistence after 2 years of treatment was still evident, suggesting that current treatments are probably not fully effective.

A still unresolved issue is the standardization of monitoring parameters. Another main challenge is represented by the identification of the best tophaceous deposition candidate to be the most representative target for follow-up morphological analysis. What we still do not know is the dynamic of the crystal-clear process at different anatomical areas. It would be logical to keep under control tophaceous deposition at joint cartilage and tendon levels. A final target of US monitoring in these patients is to evaluate the relationship between the density of tophaceous material and the crystal-clear process at different anatomical sites.[33]

Usefulness in clinical practice: Reliability and feasibility

Musculoskeletal US has gained notable recognition among imaging modalities used in the assessment of gouty arthritis due to its ability to visualize not only soft tissue inflammation and joint damage, but also MSU crystals.

Current accessibility to sonography may better classify patients with hyperuricemia and gout and contribute to delineating therapeutic objectives and clinical guidance. Our understanding of the natural history of gout has improved in the last decade, in particular the identification of a continuum between a preclinical state defined by asymptomatic MSU crystal deposition within joints and tendons, and occurrence of the first gout flare has been facilitated by the use of novel imaging such as US and DECT.

Different studies have recently addressed the role of US in gout. They evaluated not only the different lesions to be searched, but also the sites to be investigated in order to improve the sensibility and specificity of the technique, the detailed changes that can be detected by US as well as the response to therapy.[3,25,28]

Table 3. Utility of US in gout.

Gout diagnosis	
Patients with arthritis and hyperuricemia	Double contour +++ Tophus +++ Hyperechoic spots Erosions
Patients with asymptomatic hyperuricemia	
Differential diagnosis	CPPD ++
Localization and aspiration of joint effusion	
Treatment strategy	
Introduction of urate-lowering therapy	
Duration of preventive treatment of acute flare	
Quantification of urate deposits and follow-up after treatment	Disappearance of DCS
Synovitis quantification	Doppler signal

US can identify the site to perform the aspiration or the biopsy and can make the procedure easier and safer. Moreover, intraarticular corticosteroid injection is considered an effective and safe therapeutic option in acute gouty arthritis, when nonsteroidal anti-inflammatory drugs and oral therapy are not tolerated, not effective, or contraindicated. US guidance enables a more accurate and safe procedure.

Chowalloor and Keen[34] published a systematic review focused on the validity, reliability, responsiveness, and feasibility of US-detected alterations not only in gout but also in asymptomatic hyperuricemia. US is able to detect tophi, using MRI as the gold standard, and is sensitive to change. The DCS seen overlying cartilage is specific to gout and sensitive to change. Synovial pathology is identified in gout, with some reporting intrasynovial hyperechogeneicity is suggestive of gout. US was less sensitive than MRI to cortical erosions in gout, but better than conventional radiography. Interobserver reliability when assessed ranged from fair to substantial agreement for soft tissue changes and was very good for assessing tophi, double contour, and erosions.

In this order of ideas, Durcan et al.[35] published also a systematic literature review of imaging modalities for gout. All clinical features were addressed with US, including joint damage, urate deposition, and inflammation, with data regarding truth and discrimination for all three domains. The feasibility and reliability of US are also analyzed, finding that US can be performed in the clinic and while US machines are relatively inexpensive, the time and training costs are considerable.

Conclusions

The observation of MSU crystals is still required to provide an unequivocal diagnosis of gout however this is often not possible.

Imaging techniques have several applications in the diagnosis, clinical monitoring, and management of the disease but, particularly, musculoskeletal US is a useful, noninvasive tool that is able to detect microcrystal aggregates in multiple anatomic areas of asymptomatic individuals with hyperuricemia and gouty patients.[33] Also, US can be used as a safe and reliable guide to aspirate even minimal fluid collections suitable for microscopic analysis,. And it can also be used as a tool for monitoring monosodium urate crystal dissolution induced by ULT (Table 3).[36] The first metatarsophalangeal joint and the knee should be regarded as the anatomic regions with the highest probability of being, respectively, positive for monosodium urate aggregates.[37]

However, further work is required, particularly with regard to the currently large gaps in the published literature that limit the assessment of gout imaging. A possible future research agenda would be to perform longitudinal studies (observational or prospective) that include imaging assessment of gout, in order to document the radiographic natural history or response to therapy; to perform prospective studies on the performance of US as a diagnostic tool when applied to the setting of acute arthritis in real-life practice, since many studies have been performed in patients with established disease; to perform studies comparing imaging findings with a pathological or imaging gold standard for most analyses, and studies searching data relating to the patient experience or acceptability.

Calcium pyrophosphate deposition disease (CPPD)

Calcium pyrophosphate crystal deposition disease (CPPD) according to the definitions of EULAR in 2011[38] refers to the spectrum of clinical manifestations associated with crystal deposition in the joints. Such deposition can precede clinical manifestations by even years, making diagnosis difficult. Synovial fluid (SF) detection of calcium pyrophosphate crystals (CPP) by polarized light microscopy is considered the gold standard for the diagnosis of CPPD.[38] However, SF is not always available for analysis, and accurate detection of CPP crystals can be difficult and with highly variable sensitivity.

There is some confusion regarding the nomenclature, the term "pseudogout" has been classically used to describe episodes of acute arthritis induced by CPP crystals. Chondrocalcinosis (CC) refers to radiographic or histological calcification of hyaline cartilage or fibrocartilage. It is present in patients with CPPD but it is not absolutely specific nor does it appear in all affected cases.[38]

CPPD is one of the most common arthropathies and clearly increases with aging, with a highly variable prevalence—from 4 to 50%—depending on the diagnostic method used.[39] The prevalence of CPPD is on one hand considered to be underestimated by the frequency of asymptomatic cases. And, on the other hand, radiographic CC is not absolutely specific for CPPD and may confuse the actual prevalence.[40]

The formation of CPP crystals begins in the extracellular matrix of the cartilage and its deposit is due to a local supersaturation of CPP. The transmembrane transport of CPP is regulated by the ANKH protein. Once CPP crystals are generated, they induce tissue damage and inflammation by activating components of NLRP3 (inflammasome and extracellular neutrophil traps). They also produce direct catabolic effects on chondrocytes and synoviocytes, accelerating joint damage.[41]

An interesting topic is the relationship between CPPD and osteoarthritis (OA). There is a controversy as to whether OA and CPPD can be associated or if they could be different diseases but with a common risk factor, aging.

A meta-analysis[42] showed a powerful association between knee CC and OA. Although they included studies of CC (not confirmed by CPP crystals in SF), which is an important limitation.

Another recent study[43] with US demonstrated a higher degree of synovitis in the knees of patients affected by CPPD (confirmed with SF crystals) compared to isolated OA. But no differences were found regarding osteophytes and cartilage damage in both groups. The authors considered it reasonable to suppose that they are two different diseases in a group of patients at common risk.

Another known discussion is the association of CPPD and rheumatoid arthritis (RA). In a recent

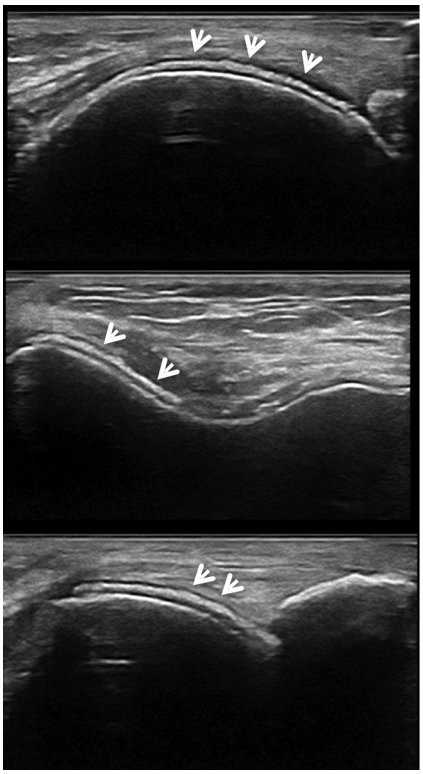


Figure 13. Knee hyaline cartilage CPP deposits (arrows). Hyperechoic (similar to the cortical bone echogenicity) without posterior acoustic shadow localized within the hyaline cartilage.

review,[44] they have raised the difficulty of differential diagnosis between polyarticular forms of CPPD and seronegative RA in elderly patients with CPP crystals in SF. These same authors described the efficacy of methotrexate in elderly patients with symmetric RA-like synovitis and CPP crystals in SF. Since other clinical forms of CPPD do not respond to methotrexate, it seems more likely that they are RA and CPP crystals are only an incidence. Similar conclusions have been presented by another study in patients with RA and CPPD in which the diagnosis of RA preceded years (mean of 13.4 years) to that of CPPD in most cases. The classic age of CPPD onset and the typical pattern of joint involvement suggest that CPPD and RA would be coexisting pathologies and not by direct association.[45] The review authors suggest the utility of imaging for the detection of lesions characteristic of RA or in detecting extensive deposition of CPP crystals.[44]

Imaging in the diagnosis of CPPD

Although the gold standard is the identification of CPP crystals in SF, the diagnosis of CPPD has been based on imaging techniques, especially on conventional radiography (CR).

The CR shows the deposition of CPP crystals in the radiological joint space at the level of the cartilage and fibrocartilage. CC is a useful image marker, but it is a surrogate sign of CPPD. The EULAR review evidenced a frequent discordance between CR and the identification of crystals in SF. This is attributed to the lack of CC specificity for CPPD (basic calcium phosphates can also cause it), the low sensitivity of CR when there is cartilage loss, and the difficulty in identifying minimal amounts of CPP crystals.

The EULAR recommendations of 2011 suggested that radiographic CC supports the diagnosis of CPPD, but its absence does not exclude it.[38]

Magnetic resonance imaging offers great anatomical detail, but calcified tissues are poorly visualized. Conventional computed tomography has been widely used in the involvement of the spinal column in CPPD, especially in the atloaxoid condition (crowned dens syndrome). However, it is DECT that has generated more interest in CPPD in recent years, due to its usefulness in gout. Promising data have been reported on the ability of DECT scans to identify chondrocalcinosis, but more data is required from studies comparing DECT with CPP crystals in SF, as the gold standard for CPPD.[40]

Ultrasound in the diagnosis of CPPD

In the early 2000s when technical improvements allowed for higher ultrasound image resolution, Grassi et al.[46] described the typical appearance of CPP crystals. Distinctive features of US included crystal deposition inside articular hyaline cartilage (HC), fibrocartilage (FC), and tendons.

Since then, many studies have been carried out with enough evidence and in 2011 EULAR experts published the recommendations of CPPD recognizing the US as a useful diagnostic method for CPPD.[38] These recommendations refer to the usefulness of the US to detect CPP deposits in the knees, wrists, and shoulders. The evidence for sensitivity and specificity was excellent, and even more sensitive than radiographs in detecting CPPD. The presence of US findings has been strongly associated with the diagnosis of CPPD (LR = 24.2, 95% confidence interval = 3.51-168.01).[47] The suitability of US varies between anatomical locations, with low sensitivity in deep structures such as the spine.[38] The extent and distribution of CPP crystals in the joints have also been studied using US, with the knee being the most frequently involved site.[48]

Ultrasound findings of CPPD: Elementary lesions

In 2014 the OMERACT Ultrasound and CPPD working group was created due to the diagnostic potential of the US and the need for standardization and validation of the technique. The lack of consensus in the definitions of the US findings limited the comparability of the studies.

Following the OMERACT methodology, the US definitions were agreed according to the opinion of experts through a Delphi exercise.[39]

These definitions include the characteristics of the CPP deposition according to the anatomical structure: Hyaline cartilage (Figure 13), fibrocartilage (Figure 14), tendon, and SF. In each anatomical site, the shape, echogenicity, location, and behavior of the deposits in the dynamic examination are described (Table 4).

Subsequently, the intra- and interobserver reliability of the definitions was evaluated using a web exercise with static images (method with limitations) and another face-to-face exercise with patients (more accurate and similar to real life). This exercise evaluated HC, meniscus (FC) and tendons of the knee, triangular carpal fibrocartilage (TFC), and SF.

The findings in HC and FC of the knee showed the highest values of interobserver reliability, both in web exercise (kappa 0.73 for HC and 0.58 for FC) and with patients (kappa 0.55 for HC and 0.64 for FC). The kappa values for other structures were lower, from 0.28 in tendons to 0.50 in SF in the web exercise and from 0.09 (in tendon) to 0.27 (TFC) in the patient exercise.

These definitions showed good knee reliability but low in other locations,[39] therefore, another US reliability study[49] was conducted using the OMERACT definitions on wrist (TFC), metacarpophalangeal (MCP), acromioclavicular (AC), and hip joints. Previous web-based exercise and patient image acquisition methodology were followed.

The inter and intraobserver kappa values were high for the TFC of the wrist (0.75-0.87 good to excellent) followed by the AC joint (0.51-0.85 moderate to excellent). Detection of CPPD in the hip, tendons (quadriceps and patellar), or SF (in the knees or wrists) showed insufficient reliability inter readers. The divergent results in TFC reliability in both studies (kappa 0.27-0.82) could be attributed to the fact that in the second study the US scanning techniques were previously homogenized, improving their reliability.

An atlas of US CPPD images was published as a pictorial example to be used as reference.[49]

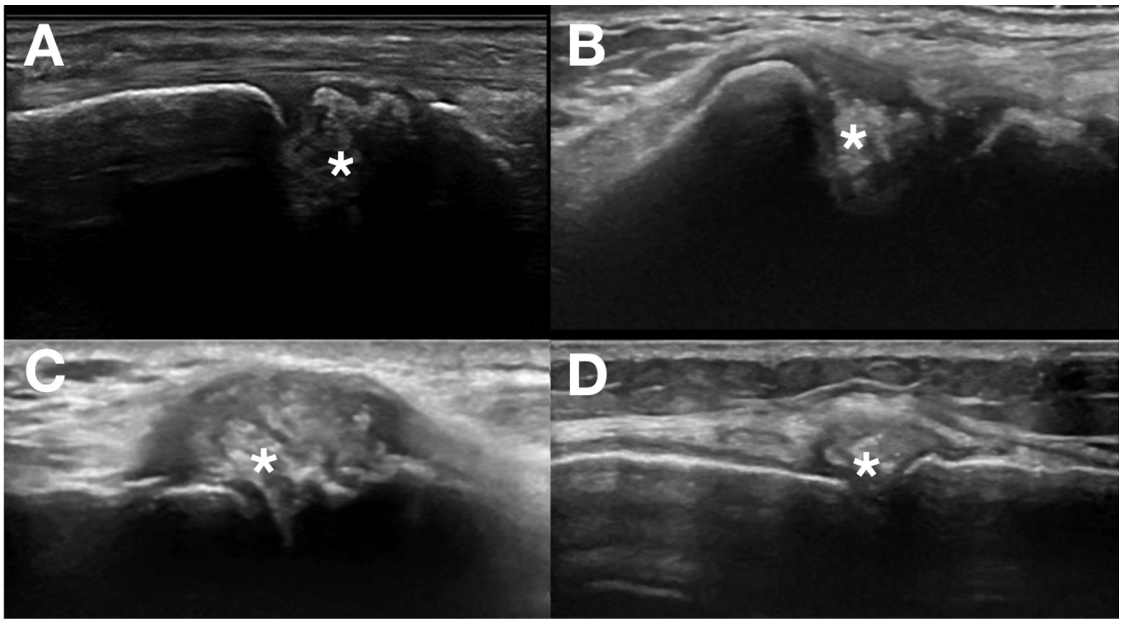
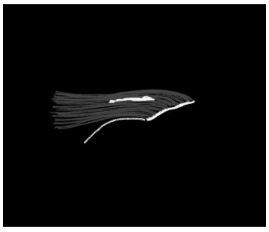


Figure 14. A-D. (A) and (B) Hyperechoic aggregates in carpal triangular fibrocartilage characteristic of CPPD (*). (C) Aggregates in fibrocartilage of the acromioclavicular joint. (D) Aggregates in the meniscus of the knee.

Table 4. Definition of elementary ultrasonographic findings in calcium pyrophosphate deposition disease (OMERACT).

Structure	Shape	Echogenicity	Localization	Behavior at dynamic scanning (Joint movement and probe compression)	Example US
Fibrocartilage	Deposits of variable shape	Hyperechoic (similar to the cortical bone echogenicity)	Localized within the fibrocartilage structure	Remain fixed and move together with the fibrocartilage	
Hyaline Cartilage	Deposits varying in size and shape	Hyperechoic (similar to the cortical bone echogenicity) without posterior acoustic shadow	Localized within the hyaline cartilage	Remain fixed and move together with the hyaline cartilage	
Tendon	Multiple, linear (parallel to the tendon fibrillar structure and not in continuity with the bone profile) deposits.	Hyperechoic (in relation to the tendon echogenicity) that generally do not create posterior acoustic shadow. The deposits maintain their high degree of echogenicity even at very low levels of gain and are not affected by anisotropy as the surrounding tendon	Localized within the tendon	Remain fixed and move together with the tendon	
Synovial fluid	Deposits of variable size (from punctuate to large).	Hyperechoic (in relation to the tendon echogenicity) thet generally do not create posterior acoustic shadow.	Localized within the synovial fluid	Are mobile according to joint movement and probe pressure	

Modified from OMERACT definitions[39]

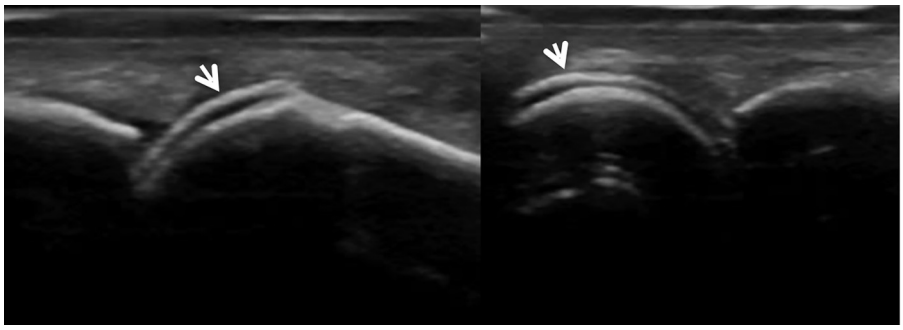


Figure 15. Patient with CPPD and double contour image in the second metacarpophalangeal joint of the hand (arrow).

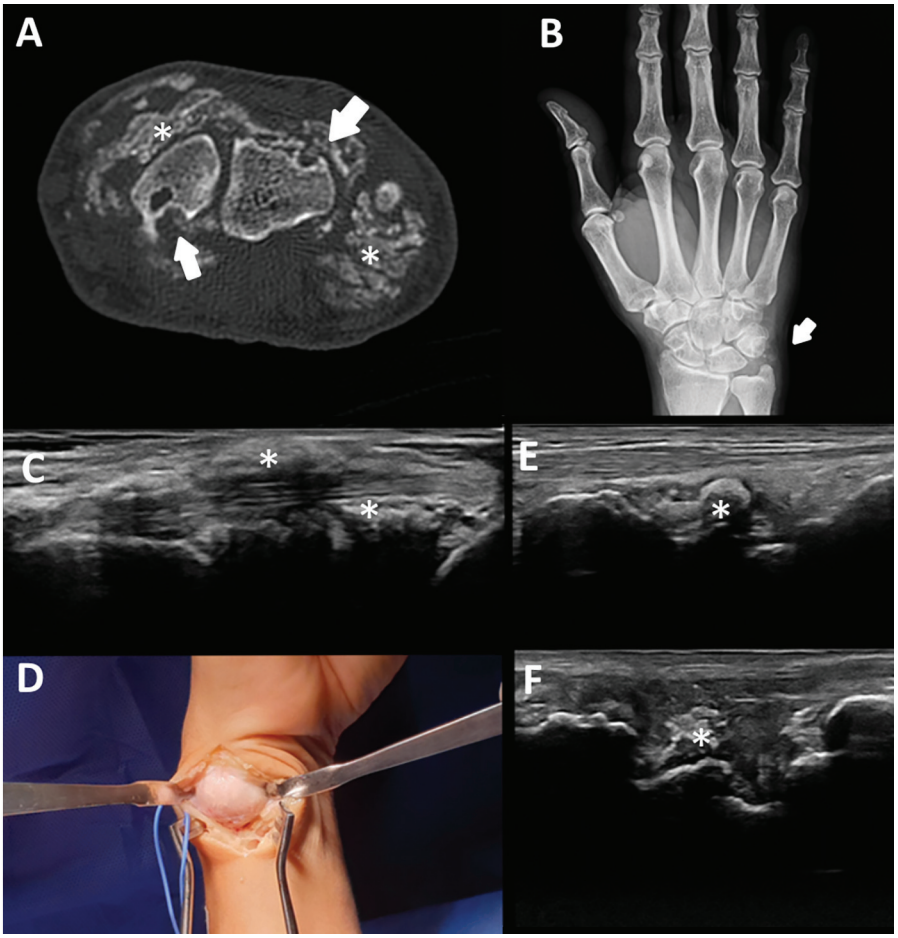


Figure 16. A-F. Patient with tophaceous or pseudotumoral CPPD in the wrist. (A) Conventional CT image showing calcium aggregates (*) and bone erosions (arrows). (B) Conventional radiography of the hand with chondrocalcinosis in the carpal triangular fibrocartilage (arrow). (C) Ultrasonographic image of carpal extensor tendons with aggregates similar to tophus (*). (D) Surgical image of the aggregates (courtesy Dr. Xavier Gonzalez), histology confirmed that they were CPP crystals. (E) and (F) Ultrasound images of the wrist with intrasynovial hyperechoic aggregates (*).

In conclusion, the OMERACT definitions of elemental lesions demonstrated high reliability at the level of the TFC, AC joint, HC, and FC of the knee, while not reaching acceptable kappa values in tendons or SF.[39,49]

A curious fact is that OMERACT definitions did not include the DCS. Although DCS has high gout specificity, it is also visible in CPPD in up to 7% of cases,[3] not only in patients with both types of crystals but also in the absence of MSU (Figure 15). Tophaceous microcrystalline aggregates (Figure 16) were also not included, which are observed in at least 5% of cases of patients with CPPD.[3]

Usefulness in clinical practice: Reliability and feasibility

To date, US is the most validated method for diagnosing CPPD, since it has been shown to be reliable and capable of discriminating CPP deposition in the FC and HC of the joints. US studies in CPPD have evaluated different locations, including knees, wrist, hip, and shoulder. Study designs are variable (cohort studies, control cases) and the diagnosis of CPPD has been made more frequently by SF analysis, and in some cases by clinical or histology. The US has been compared with the gold standard of crystals in SF, and in some studies with radiology or histology.

The US compared with CPP crystals in SF, has shown in two meta-analyzes[50,51] a high diagnostic performance, with a sensitivity of 88% and a specificity of 92%.[50] Considering the anatomical structures, a higher diagnostic accuracy was observed for HC (77% sensitivity and 92% specificity) followed by FC (77% sensitivity and 96% specificity); however, tendons and entheses showed weaker results.[51]

In another study of diagnostic accuracy of US in knees that underwent prosthetic surgery, US was compared with CR, SF crystals, and histology. US proved to be a technique at least as accurate as SF crystals for the diagnosis of CPPD, with sensitivity and specificity values of 96% and 87% for US, 75% and 93% for CR, and 77% and 100% for SF, respectively.[52]

At the recent EULAR 2020 congress, the OMERACT group has presented diagnostic accuracy data from the US in CPPD.[53] In 68 patients with OA undergoing knee arthroplasty, US was compared with histology of meniscus and cartilage. CPPD was diagnosed in 34 cases according to microscopy. The US demonstrated high diagnostic accuracy for CPPD and the best site was the medial knee area (HC and FC) with a sensitivity of 0.88, specificity 0.76, diagnostic accuracy 0.82, PPV 0.79, NPV 0.87.

In validation studies of US compared to CR, in general, US is more sensitive than CR to diagnose CPPD. Ottaviani et al.[54] and Ruta et al.[55] compared US and CR regarding the detection of crystals in SF. The sensitivity for US was 60-100% and specificity 92.3-96.7% compared to 40-64% and 83.3-100% for CR. In another study, Forien et al.[56] compared US and carpal

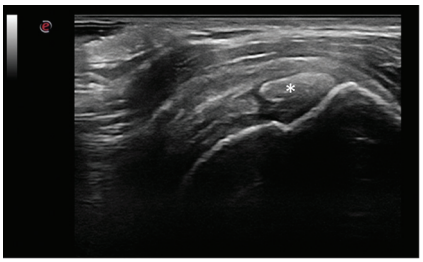


Figure 17. Longitudinal ultrasound image of the supraspinatus tendon with an aggregate of crystals of basic calcium crystals (*).

CR in 32 patients with crystals identified in SF. The US also showed a higher sensitivity (94%) than CR (53.1%) to detect CPP deposits.[56]

However, Di Matteo et al.[57,58] recently reported comparable sensitivities (77.8-90% for US, 76.4-86% for CR) and even slightly better specificity for CR (90-96.9% vs 85-90.6% for US) to detect CPPD in carpal TFC and in the hip. In general, studies suggest that the detection of chondrocalcinosis in CR may require a higher crystal load, and this would place US as an early diagnosis technique.

An independent study by Lee et al.[59] confirmed the excellent reliability and diagnostic precision of the OMERACT definitions in knee comparing US, CR, and SF crystals. US detection of CPPD in FC and HC showed a sensitivity of 70% and a specificity of 79% vs 44% and 97%, respectively, on conventional radiography.

The anatomical sites to be explored and the feasibility of the exploration is an issue not yet resolved. The anatomical distribution of crystal deposits can be used to distinguish MSU crystals from CPP crystals, as confirmed in studies focused on gout patients. Nor has a crystal deposit quantification system been defined. In 2013, a semiquantitative US score was proposed for the extent of CPPD deposition in fibrocartilage and hyaline cartilage,[47] and has even been used in recent studies[56,57] but has not yet been fully validated for use in practical clinic.

In conclusion, the US showed its diagnostic utility in CPPD, especially in the knee and wrist, with a sensitivity of 0.60-1 and specificity of 0.76-0.96. Good reliability has also been demonstrated among readers both in the knee (kappa 0.55-0.73) and in TFC (kappa 0.27-0.75) and high intrareader reliability (kappa 0.80-0.81 in the knee and 0.82 in TFC).[39,52]

Regarding the sensitivity to change of the US in CPPD, in the absence of an effective treatment for CPPD, it has not yet been established.

Conclusions

- US has been validated in a more accurate way than other advanced imaging techniques, being the first choice for diagnosis of CPPD. It has also been demonstrated as a more sensitive technique in detecting CPPD than CR.
- Consensus definitions of the characteristic US lesions of CPPD have been developed and have been partially validated.
- The anatomical sites of microcrystalline deposition are a key factor for differential diagnosis in microcrystalline arthropathies
- The future research agenda should include the evaluation of other US lesions, feasibility of exploration of specific sites, and validation of deposit extension scoring systems for clinical follow-up.

Other crystal-related arthropathies: Basic calcium arthropathy (BCP)

Basic calcium phosphate crystals (BCP) are associated with two musculoskeletal syndromes.

On one hand, deposits of BCP crystals in tendons, bursae, and periarticular structures cause periarthritis or calcium tendinopathy, very frequent in the shoulders and trochanteric region (Figure 17). On the other hand, intra-articular BCP crystals are associated with OA and destructive arthropathy (Milwaukee Shoulder Syndrome). The role of US in calcium tendinopathy has focused on interventionism, since it allows the performance of percutaneous US-guided therapies with aspiration and washing of microcrystalline deposits or *barbotage*. It is a safe technique, effective in the short and long term, slightly invasive, and, in many cases, avoids surgical treatment.[60]

In BCP arthropathy, a recent review concludes that there are limited data on the utility of US in differentiating the crystals of BCP and CPP.[61] In addition, as in gout and CPPD, a US definition is required and its subsequent validation process.

At the articular level, BCP crystals, like CPPD, have been related to OA. In the study by Frallonardo et al.,[62] they compared the presence of CPP and/or BCP crystals in SF in patients with knee OA regarding clinical symptoms and US synovial inflammation. 110 patients were included and 23.6% of them had CPP crystals, 21.8% of BCP, and 6.3% both types of crystals. The prevalence of CPP alone (27.8%) or in combination with BCP (11.1%) was higher in the advanced OA group, but the prevalence of isolated BCP crystals was higher in early OA. Furthermore, both types of crystals were associated with synovial inflammation evidenced by US. The results of this study suggest a role for calcium crystals in the development of early OA.

Conclusion

Although the gold standard for diagnosing gout and CPP arthritis is the identification of crystals in joint fluid, the US features of both pathologies have been well described. US has been proposed as a convenient diagnostic tool for crystal-induced arthritis, as well as to assist in clinical management, monitoring disease activity, and therapy response.

Is considered the most operator-dependent imaging technique, hence in the hands of an experienced rheumatologist, a multisite, tissue-oriented and clinically driven US examination represents a feasible and powerful approach to obtain valuable clues in the suspicion of microcrystalline arthritis in daily clinical practice.[63]

In the past, US has therefore evolved from being an examination to understand merely what is occurring in a specific anatomical site to being used to determine what is occurring at the systemic level in patients.

Nowadays, US is increasingly helpful in daily clinical practice to understand the course of the disease as a whole. It has become an important and helpful tool for the diagnosis and assessment of several inflammatory diseases, including the microcrystalline arthropathies, and it has therefore become a valuable part of the therapeutic decision-making process.

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