Chapter

Musculoskeletal and Nerve Ultrasonography

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Abstract

Musculoskeletal ultrasound had gained more and more importance lately and there is no doubt now about its role in the diagnosis and management of rheumatic diseases such as rheumatoid arthritis, spondyloarthritis, osteoarthritis and crystal related arthropathies. We can say that now, US is a widely available, non-invasive, and cost-effective technique suitable for the evaluation of the articular and periarticular structures, such as joints, tendons, muscles, ligaments, and bursa. The real-time capabilities of the US allow continuous observation of those structures during movement and of the needle placement during musculoskeletal interventions. More than this, recently, ultrasonography (US) has gained its rights in the evaluation of Sjogren syndrome and giant cell arteritis. Thus, US can detect changes secondary to both inflammatory joint diseases, like synovitis, tenosynovitis or enthesitis, and to degenerative disease, like osteophytes or tendinosis. US can identify calcium pyrophosphate and urate deposits at the level of the cartilage and tendons and to recognize the changes at the level of the salivary glands in the context of the Sjogren's syndrome and the ones at the level of the temporal artery, secondary to giant cell arteritis.

Keywords: rheumatology ultrasound, musculoskeletal, synovitis, enthesitis, nerve

1. Introduction

Ultrasonography (US) has become an integral part of the clinical rheumatology practice. It provides relevant information in many aspects of patient management, both diagnostic and therapeutic. It is a safe, non-invasive and readily accessible imaging modality, with a lack of contraindications. In this respect, US carries significant advantages over other imaging tests, such as CT or MRI. Musculoskeletal ultrasound provides the physician with a real-time evaluation, allows for a dynamic view of target areas and simultaneous scanning of multiple anatomical structures. It is fairly easy to apply imaging techniques, although it requires a prolonged period of training to achieve expert-level assessments. Musculoskeletal ultrasound (MSUS) allows for a fast examination of small and large joints and can guide further diagnostic tests. One of the most important benefits of MSUS is early diagnosis of articular and periarticular inflammation; this is especially the case in rheumatoid arthritis and psoriatic arthritis where diagnostic delay from symptom onset can lead to significant structural progression and poor outcomes. US evaluation is included in the EULAR (European League Against Rheumatism) recommendations for use of imaging in

disease management for both RA and Spondyloarthritis (SpA) [1, 2]. Also, standardization of US procedure is provided through the EULAR standardized procedures for US imaging [3] and OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) definitions of US pathology [4]. Apart from inflammatory and degenerative joint disease, US can also aid the rheumatologist in the diagnosis and management of connective tissue diseases such as systemic scleroderma, Sjögren's syndrome or vasculitis [5–7].

2. Principles of ultrasound examination in rheumatology

Ultrasonography enables detailed examination of anatomical structures, periarticular soft tissue and also blood flow using Doppler modalities. The 2017 EULAR standardized procedures for US [3] recommend the use of high-resolution linear transducers with a working frequency between 6 and 14 MHz for deeper structures and a frequency of ≥15 MHz for superficial areas. Probe compression can be used to distinguish compressible from non-compressible tissue, but should be avoided when examining blood flow. Images acquired in the long axis should be oriented with the proximal aspect to the left of the screen, while in the short axis, the structures of interest will be aligned just as the examiner is looking at the patient.

US evaluation can assess bone surface, cartilage, tendons, ligaments, synovial proliferation and bursal effusions. Additionally, soft tissue US will include examination of blood vessels, skin, adipose tissue, peripheral nerves for entrapment or tumors (**Figure 1**) and muscles that can be scanned for inflammation, lesions or fluid collections [8].

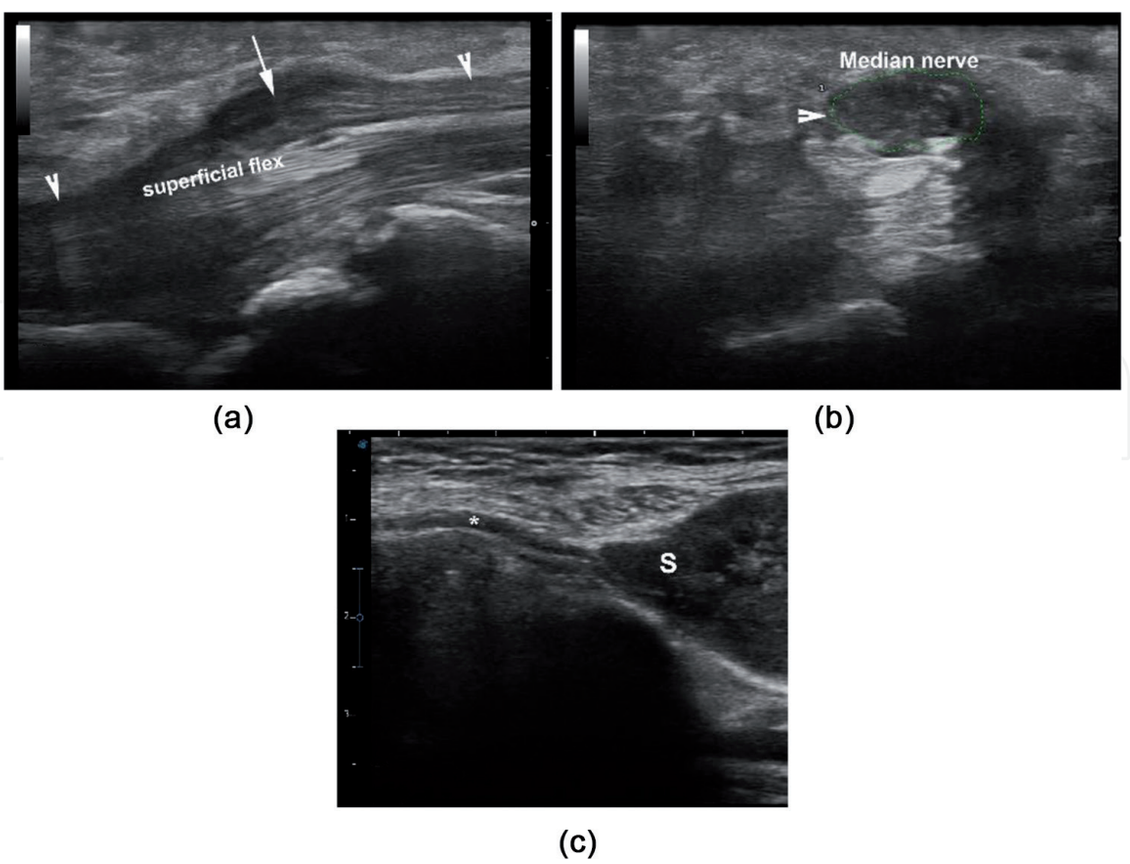


Figure 1.
Ultrasound GS images of a median nerve neuroma (a – Longitudinal, b - transverse) and a peroneal schwannoma (c - longitudinal). Arrowhead – Median nerve, arrow – Neuroma, asterisk – Peroneal nerve, S – Schwannoma.

The study of blood flow is important in detecting inflammatory activity and this can be performed using color Doppler or power Doppler modalities [9]. Because in the musculoskeletal US, the blood flow is very slow in the small new vessels formed by inflammatory angiogenesis, the pulse repetition frequency used is low, under 1KHz. Nevertheless, some small vessel blood flow is difficult to detect because the signal intensity can be lower than movement artifacts and will be filtered out [10].

Ultrasonography is examiner-dependent, thus a good clinical experience, knowledge of anatomy, good image acquisition and reading of the ultrasound images, together with pitfalls recognition are needed requirements for a quality examination. The OMERACT task-force group has developed standardized definitions to promote uniformity between US examiners' reports (see **Table 1**).

Additional information during US imaging can be obtained through sonoelastography and contrast-enhanced ultrasonography (CEUS) [11–15]. These two US techniques have been studied and proven their usefulness in certain rheumatic diseases, but nevertheless, they are not so widely used as conventional gray scale (GS) and Doppler modalities. Sonoelastography is used for measuring and quantifying tissue stiffness. This can be applied in various situations such as tendon lesions, myositis, and analysis of soft tissue formations such as gout tophi or rheumatoid nodules [16, 17]. Also, promising results are seen in studies of systemic scleroderma, where skin involvement is correlated with loss of dermal elasticity [5]. CEUS can assess joint inflammation and provides a view of the exact vascular patterns, which can also be visible in inflamed sacroiliac joints [10, 18]. Some studies report the superiority of CEUS compared to power Doppler US in detecting synovial hypervascularity [14, 15]. Compared to the known risks of using contrast agents in MRI and CT, contrast agents used in CEUS have no proof of significant side-effects.

Further use of ultrasonography in rheumatology practice resides in the ability to guide local procedures. These include synovial fluid aspiration, therapeutic injection, nerve blocks or soft tissue biopsy [19]. US guided infiltrations have proven to significantly increase the accuracy of medication placement when compared to infiltration guided by anatomical landmarks [20]. This is also the case in aspiration of small fluid effusions or fluid cavities which have multiple septa. Besides the accuracy of therapy injection, US-guided procedures have a reduced risk of damaging nearby nerves, tendons or blood vessels.

Bone Erosion	A step-down intraarticular discontinuity of the bone surface is visible in 2 perpendicular planes.
Synovial Fluid	Abnormal displaceable and compressible, hypoechoic or anechoic (in comparison to subdermal fat) intraarticular material, that does not exhibit Doppler signal. To note that sometimes it may be isoechoic or hyperechoic
Synovial Hypertrophy	Abnormal non-displaceable, but poorly compressible, hypoechoic intraarticular tissue (relative to subdermal fat), that may sometimes be isoechoic or hyperechoic. The Doppler signal might be present.
Tenosynovitis	The thickened tendon sheath, with hypoechoic or anechoic material inside, which is seen in 2 perpendicular planes, and which may exhibit Doppler signal. Also, fluid might be present.
Enthesopathy	Thickened tendon or ligament at its bony attachment, with loss of normal fibrillar architecture, looking abnormally hypoechoic (may contain calcifications, seen as hyperechoic foci and/or bony changes including enthesophytes, erosions, or irregularity), identified in 2 perpendicular planes. It may exhibit a Doppler signal.

Table 1.
OMERACT definitions of ultrasound lesions [4].

Despite being highly sensitive to inflammatory features, sometimes US cannot discriminate between underlying diseases, especially when suspecting septic arthritis. Here, arthrocentesis can aid the diagnosis through fluid analysis in Gram stain, culture, as well as polarized microscopy.

3. Pathology

3.1 Rheumatoid arthritis

Musculoskeletal ultrasound is frequently used in clinical practice when approaching a patient with joint pain or during the management of a patient with an established diagnosis of RA. US examination can provide valuable information and is often essential for differential diagnosis. Gutierez et al. established in a study on 204 patients with undifferentiated arthritis that US can help fulfill the ACR 2010 criteria and led to a modified diagnosis in 42.1% of cases [21]. This is very insightful because it points out to a significant proportion of patients, mainly seronegative cases with limited joint involvement that could be underdiagnosed within the first months from symptom onset. The 2013 EULAR recommendations for imaging in RA have taken this into account and highlighted the importance of early detection of inflammation and structural damage in patients with arthritis in at least one joint [1]. 9 out of 10 recommendations included the use of ultrasound. This stands for the potential benefit of US in the whole disease spectrum: detection of subclinical inflammation, prediction of progression, differential diagnosis and disease monitoring [22, 23].

The US features seen in RA include: synovial proliferation, joint effusion, cortical bone erosions (**Figure 2c** and **d**) and tenosynovitis. Among these, the presence of erosions and synovial proliferation are considered more specific (**Figure 2**). Moreover, synovial thickening with an increased power Doppler signal can differentiate between active and inactive inflammation [24]. The presence of active inflammation on US and bone marrow edema on MRI can predict risk for radiological progression even in asymptomatic joints. The potential for predicting erosive damage has also been proven for features of tenosynovitis [25].

There is significant evidence related to residual inflammation in clinical remission which in this case could be considered an unstable remission [26]. This can predict a disease flare or structural damage in asymptomatic cases within one year [27].

A more accurate evaluation of inflammatory features detected in RA patients will include a semi-quantified scoring system. This has proven to be correlated with disease activity and can aid the clinician in follow-up visits. The OMERACT study group provided grading systems for synovitis in both gray scale and Doppler mode [4] (see **Table 2**). In 2017, the EULAR-OMERACT study group integrated them into a combined scoring system for synovitis (see **Table 3**) [28].

For practical reasons, a physician should limit the number of joints included in one ultrasound examination. The exact number of joints that should be assessed will certainly depend on clinical presentation, but some studies have provided guidance for a more efficient imaging session. Naredo and colleagues proposed the examination of 12 joints using power Doppler which can provide an overall assessment of joint inflammation. The sites included bilateral wrists, second and third MCPs, and second and third PIPs of hands and knee joints [30]. In 2009, Backhaus and colleagues proposed a more limited number of joints which formed the German US7 score. This score included the wrists, II and III MCPs and PIPs, II and V MTPs joints of the clinically dominant hand and foot [31].

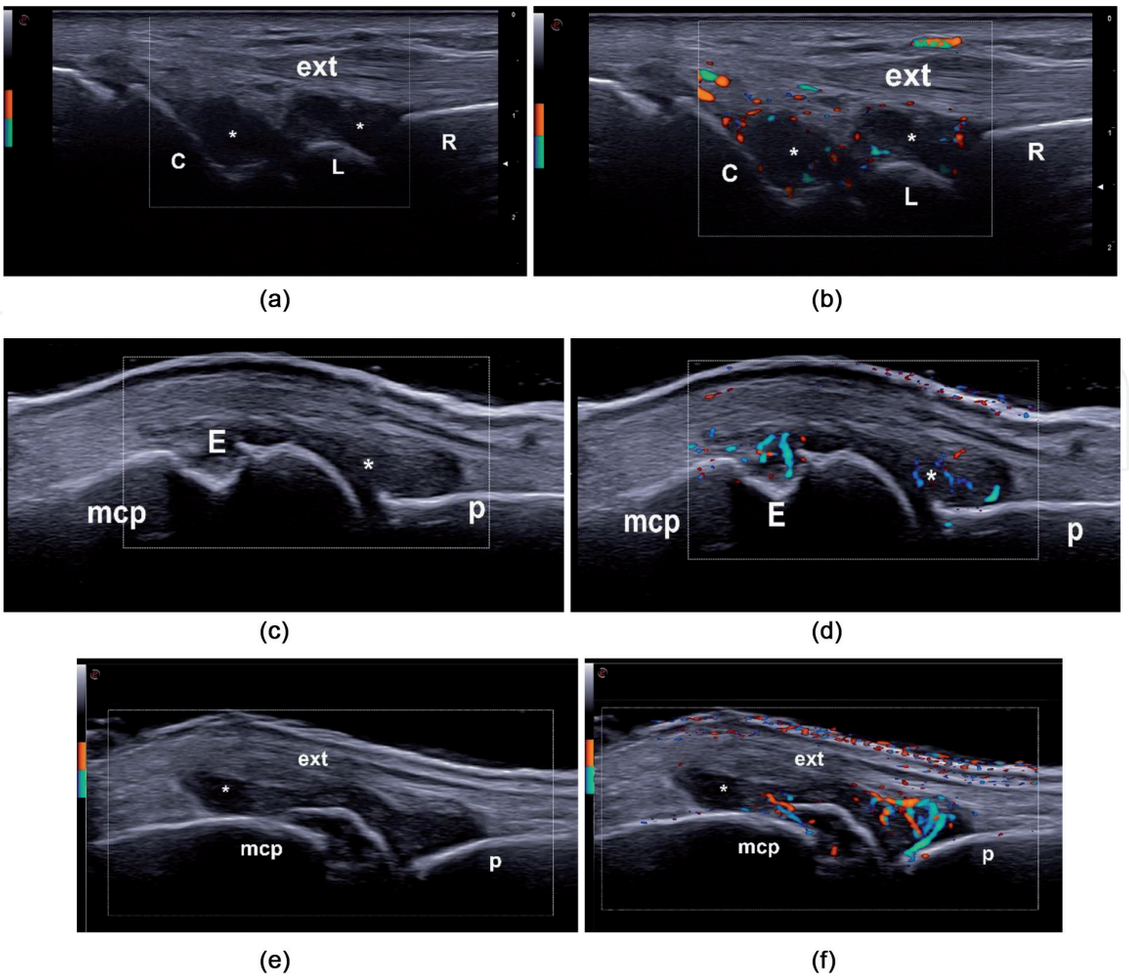


Figure 2.
Synovitis in GS (left images) and with power Doppler (right images) at the level of the wrist (a) and metacarpophalangeal joints (c-f). e – Erosions, ext. – Extensor tendons, mcp - metacarpal bone, p – Phalanx, asterisk – Synovitis.

GS	Grade 0: Normal joint (no synovial hypertrophy, no joint effusion)
	Grade 1: Minimal synovitis (minimal synovial hypertrophy, with or without minimal joint effusion)
	Grade 2: Moderate synovitis (moderate synovial hypertrophy, with or without minimal or moderate joint effusion)
	Grade 3: Severe synovitis (severe synovial hypertrophy, with or without severe joint effusion)
Power-Doppler	Grade 0: No vessels in the synovial membrane
	Grade 1: Up to 3 single color spots or 1 confluent spot plus other up to 2 single spots
	Grade 2: Doppler signal in <50% of the synovium
	Grade 3: Doppler signal in >50% of the synovium

Table 2.
OMERACT scoring system for synovitis [4].

Musculoskeletal ultrasound has proved a strong correlation with other disease activity markers such as the DAS28 score, ESR or CRP levels [32]. Nevertheless, detection of US inflammation is still possible in the context of DAS28 remission and this could influence treatment decisions [12]. US features are sensible to RA-specific

Grade 0: Normal joint	No synovial hypertrophy (SH) in GS and no PD signal (within the synovium)
Grade 1: Minimal synovitis	Grade 1 SH in GS and ≤ Grade 1 PD signal
Grade 2: Moderate synovitis	Grade 2 GS synovial hypertrophy and ≤ Grade 2 PD signal or Grade 1 SH in GS and a Grade 2 PD signal
Grade 3: Severe synovitis	GS grade 3 SH and ≤ Grade 3 PD signal or Grade 1 or 2 synovial hypertrophy in GS and a Grade 3 PD signal

SH – synovial hypertrophy; PD – power Doppler.
In addition, erosive changes have also been integrated into a 0–3 scale for each individual erosion, based on the maximum length. The scoring ultrasound structural erosion (ScUSSe) system is used as follows: 0 = no erosion, 1 = <2 mm, 2 = 2–3 mm, 3 = >3 mm [29].

Table 3.
EULAR-OMERACT combined scoring system for synovitis [28].

therapies and this has also been proven for local intraarticular steroid injections [24]. Thus, ultrasound is a helpful tool for monitoring treatment response.

3.2 Spondyloarthritis

Imaging tests commonly used in patients with axial spondyloarthritis are based mainly on the detection of sacroiliitis through conventional radiology or MRI. The use of ultrasound in SpA patients becomes relevant in peripheral involvement and especially in patients with psoriatic arthritis (PsA). US features seen in SpA patients include: arthritis, tenosynovitis, enthesitis and dactylitis. As in RA, Doppler mode is useful to confirm active inflammation in the articular and periarticular structures. Compared to RA, tenosynovitis (**Figure 3**) is more prevalent, while enthesitis and dactylitis are considered specific features of SpA.

The presence of the lesions on US can help differentiate PsA from early RA. Moreover, psoriatic arthritis patients have proven some other discriminative

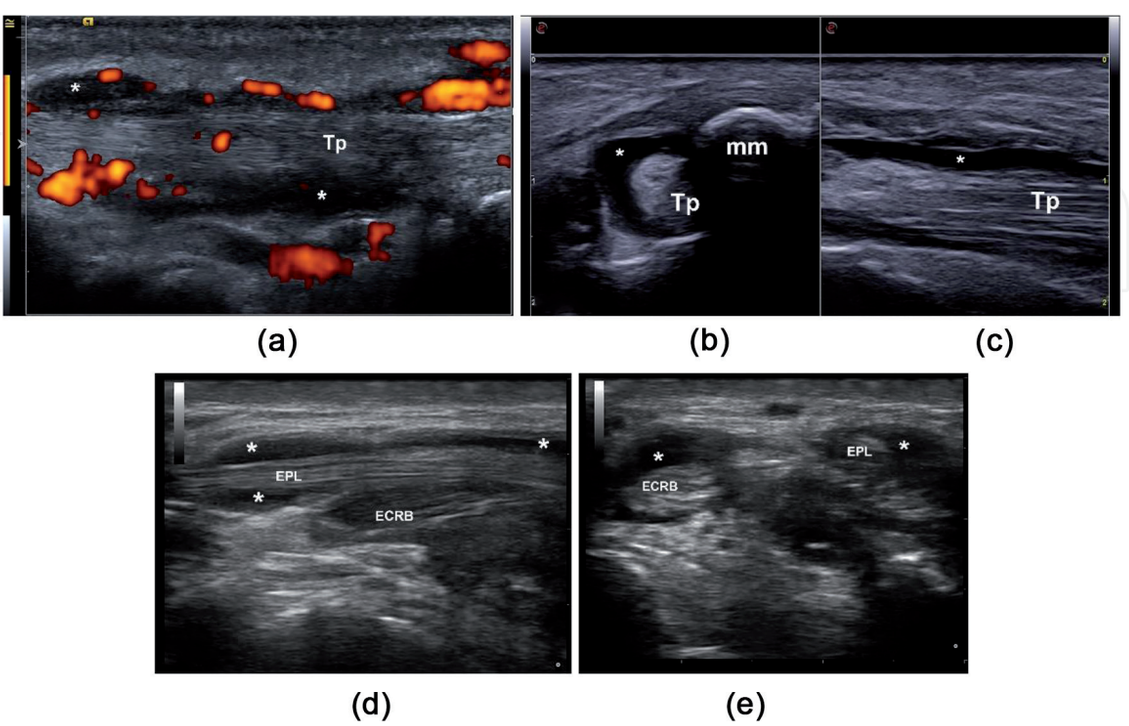


Figure 3.
Ultrasonography of the tibialis posterior (Tp) tenosynovitis (a-c, asterisk) and at the level of extensor carpi radialis brevis (ECRB) and extensor pollicis longus (EPL). mm – Medial malleolus.

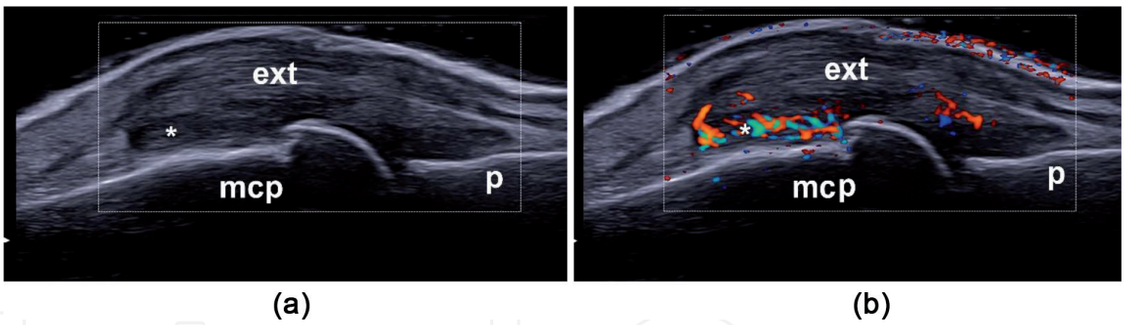


Figure 4.
Ultrasonography of the metacarpophalangeal joints in GS mode (left) and power Doppler (right), with periextensor tendon inflammation (PTI pattern - asterisk). mcp – Metacarpal bone, p – Phalanx, ext. – Extensor tendon.

features such as peritendon extensor digitorum tendon inflammation (**Figure 4**) and central slip enthesitis at the PIP joints [33].

The 2015 EULAR recommendations for the use of imaging in the diagnosis and management of SpA [2] have included ultrasound in three recommendations for peripheral SpA regarding diagnosis, monitoring activity and monitoring structural changes, as follows:

- *Recommendation 2 for peripheral SpA*

  Peripheral arthritis, tenosynovitis and bursitis may be **detected** by **US** or MRI. Furthermore, those imaging techniques may be used to detect peripheral enthesitis, which might support the **diagnosis** of SpA.

- *Recommendation 5 for peripheral SpA*

  US with high-frequency color or power Doppler and MRI may be used to **monitor disease activity** in peripheral SpA, the decision on when to repeat US/MRI depending on the clinical circumstances.

- *Recommendation 6 for peripheral SpA*

  When the clinical scenario requires monitoring of structural damage in peripheral SpA, MRI and/or **US might provide additional information**, besides conventional radiography.

The OMERACT Ultrasound Task Force published in 2013 a consensus regarding ultrasound score for tenosynovitis (see **Table 4**). A four grade-semiquantitative scoring system is proposed for both gray-scale (grade 0, normal; grade 1, minimal;

grade 0	no Doppler signal
grade 1	focal Doppler signal within the widened synovial sheath, identified in two perpendicular planes, excluding normal feeding vessels
grade 2	multifocal Doppler signal within the widened synovial sheath, seen in two perpendicular planes, excluding normal feeding vessels
grade 3	diffuse Doppler signal inside the widened synovial sheath, seen in two perpendicular planes, excluding normal feeding vessels

Table 4.
OMERACT ultrasound task force scoring system for tenosynovitis using Doppler mode [30].

grade 2, moderate; grade 3, severe) and Doppler mode (grade 0, no Doppler signal; grade 1, minimal; grade 2, moderate; grade 3, severe) [30].

Enthesitis is broadly defined as inflammation of the fibrocartilaginous tissue located at the insertion points of tendons (**Figure 5**), ligaments and the joint capsule on bone surface. US features related to enthesitis that have met the 2018 OMERACT consensus [34] include: hypoechogenicity, increased thickness of enthesis, erosions and calcifications/enthesophytes and Doppler signal at insertion. Increased tendon thickness, hypoechogenicity and shadowing of the fibrillar pattern are seen in earlier phases of enthesitis, while cortical bone changes, in the form of erosions and enthesophytes, are related to later stages [35]. Moreover, lesions should be restricted to <2 mm from cortical bone [34]. Nevertheless, distinguishing physiologic entheseal changes in active adults from disease-related lesions may be difficult. Also, lower extremity entheses are prone to mechanical loading, especially in obese patients [36].

When examining enthesis sites for inflammation, a selective approach is required. This will take into account the more accessible areas, present symptoms and potential confounding factors. Various research groups have proposed different sets of enthesis scoring systems. These include the: GUESS - Glasgow Ultrasound Enthesitis Score [37], MASEI - Madrid Sonography Enthesitis Index [38], GRAPPA US - proposed entheseal sites by the GRAPPA Ultrasound Working Group [39] and OMERACT US - proposed entheseal sites by the OMERACT Ultrasound Enthesitis Working Group [34].

New research revealed other areas in which we can find structures that can be assimilated to enthesis. Thus, we can consider as functional enthesis the areas of tendons or ligaments that are wrapped around by pulleys, without being attached to them and as articular fibrocartilaginous entheses, the synovial joints lined with fibrocartilage [40]. Inflammation of those entheses can be identified by US and can explain pain in specific areas.

Dactylitis, one of the more complex inflammatory lesions seen in SpA, is a pandigital disease that involves joint arthritis, tenosynovitis of the flexors, enthesitis of the

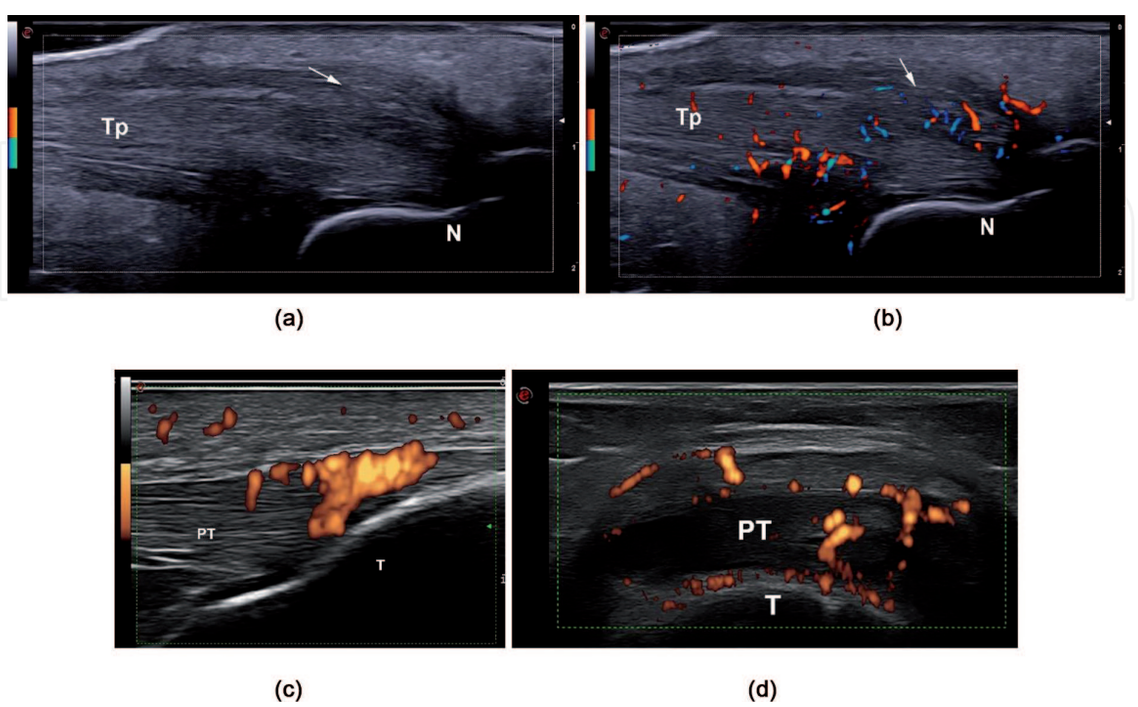


Figure 5.
Ultrasonography of the tibialis posterior (a, b – Longitudinal aspect) (Tp) enthesitis (arrow) at the level of the navicular tuberosity (N) in GS (left) and power Doppler modes (right) and enthesitis of the patellar tendon (c – longitudinal, d – transverse). PT – Patellar tendon, T – tibia.

superficial flexor of the finger, functional enthesitis, proximal to metacarpophalangeal joint (periextensor tendon inflammation) and soft tissue edema (**Figure 6**) [36, 41]. Of this spectrum of lesions, tenosynovitis (**Figure 5**) is considered the primary cause for the characteristic dactylitis or sausage-like appearance of the fingers. Flexor tenosynovitis and joint synovitis are the most frequent features seen in 90% of cases [11]. US lesions related to dactylitis evolve over time. Earlier phases are marked by tenosynovitis and lack of joint inflammation, while in later stages, joint synovitis is more prevalent in comparison to an absent or minimal tenosynovitis [42].

Dactylitis has a relevant role in the early diagnosis of PsA and has also been used as an outcome measure in clinical trials. This has prompted the development of sonographic scores for dactylitis, such as the DACTOS score. It is a composite score which includes the following: peritendinous inflammation of the extensors (PTI), evaluated in GS and PD at the MCP and PIP joints levels (with the maximum score of 4); soft tissue oedema; flexor tenosynovitis evaluated in GS and PD noted in the most severely affected area of the digit (with the maximum score of 6 for each); the combined score for synovitis (evaluated according to EULAR-OMERACT definitions) at the MCP, PIP, and DIP joints (maximum score of 9) [41]. DACTOS score is sensitive to treatment and correlates well with Leeds Dactylitis Index basic, as well as VAS for pain and functional impairment [43].

3.3 Crystal deposition disease

Gout and chondrocalcinosis are the two main forms of crystal deposition disease in which crystals of different compositions accumulate in the intraarticular space and periarticular soft tissue. In gout, raised uric acid levels in the serum to lead to deposition of monosodium urate (MSU) crystals. Chondrocalciosis, also called pseudogout, is characterized by the deposition of calcium pyrophosphate dihydrate (CPPD) crystals. Apart from the different chemical compositions, the both disorders have specific imaging features on ultrasound [17]. MSU crystals in gout generate a characteristic hyperechoic band on the cartilage surface [44], known as the "double contour sign" (**Figure 7**). The dynamic evaluation of the joint reveals the urate hyperechoic band moving together with the bone, thus confirming the belonging to the bone cartilage. This is observed in the majority of gout patients and is reversible with treatment.

MSU deposits can precipitate in the synovial membrane, in the joint cavity within synovial effusion (**Figure 8a–c**), in tendons, bursae and soft tissues. Gout tophi appear as a heterogeneous mass with intermittent hyperechoic foci and can

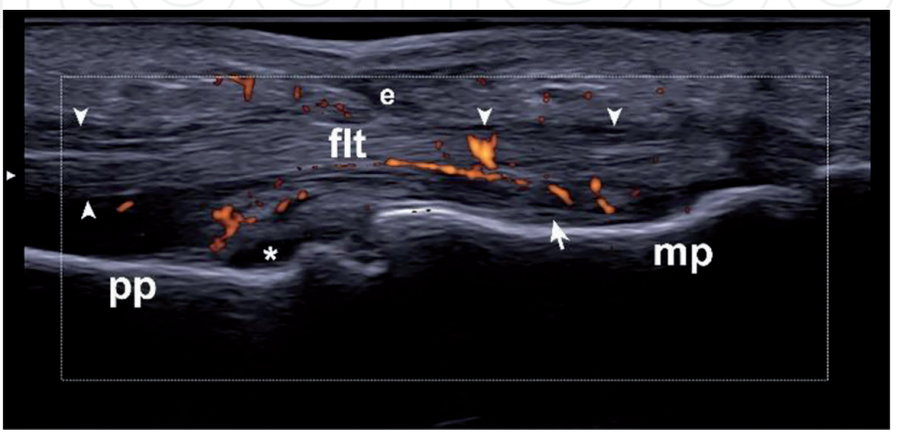


Figure 6.
Ultrasound image of a volar aspect of the finger, showing changes specific to dactylitis. pp – Proximal phalanx, mp – Medial phalanx, flt – Flexor tendon, asterisk – Synovitis, e - soft tissue oedema, arrow - enthesitis of the superficial flexor tendon, arrowheads – Flexor tenosynovitis.

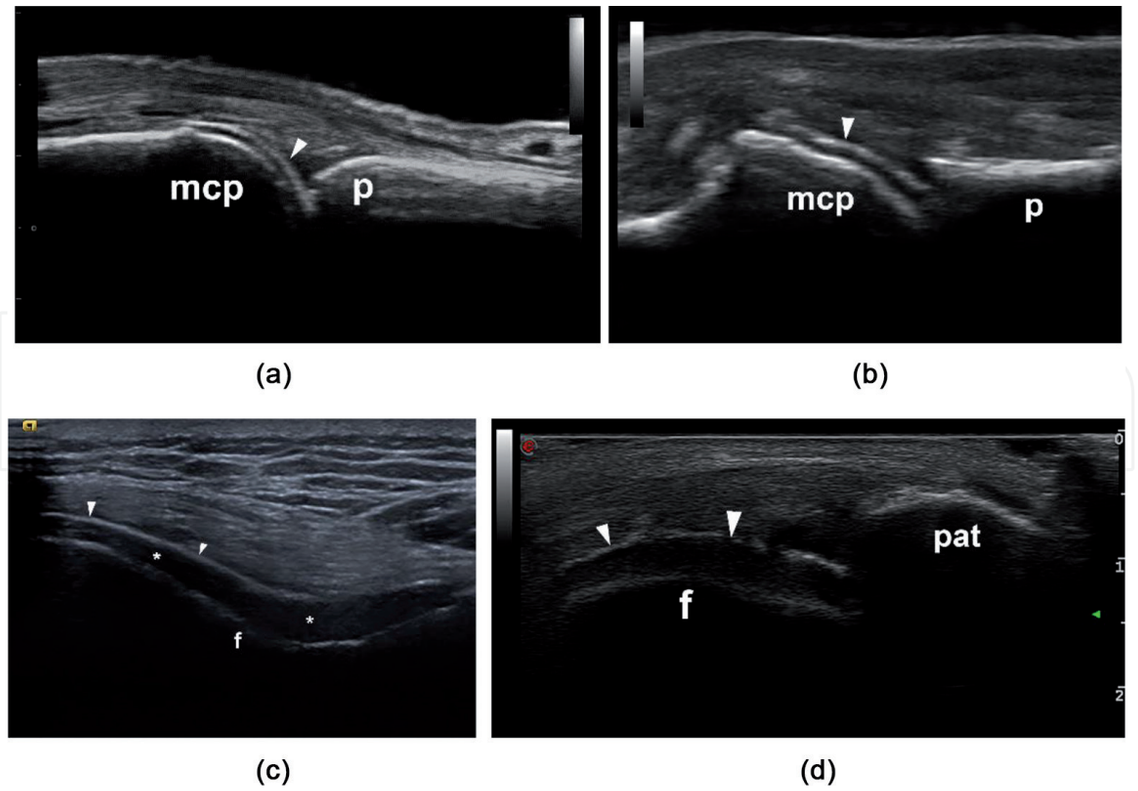


Figure 7.
"Double contour sign" (arrow head) in US of the metacarpophalangeal (a, b) and knee joints (c, d), in longitudinal (a, b, d) and transverse section (c). mcp – metacarpal bone, p – phalanx, f – femur, pat – patella, asterisk – hyalin cartilage.

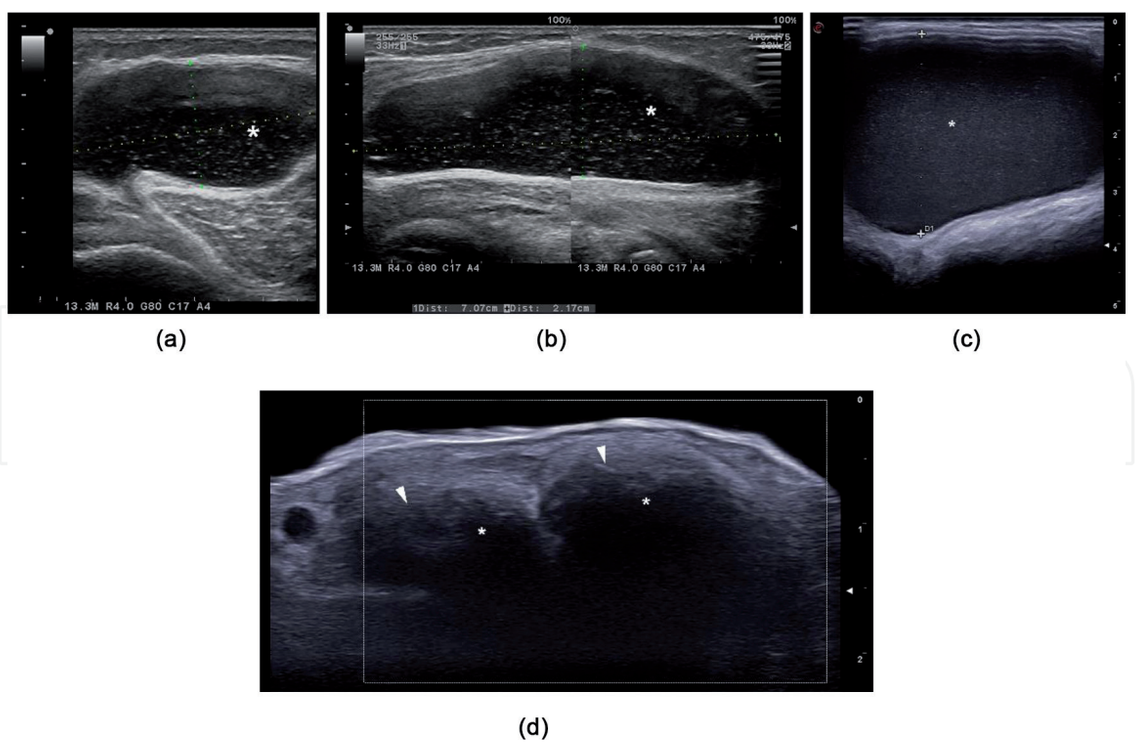


Figure 8.
a–c. Ultrasound images of gouty synovial effusion at the level of the posterior knee – Popliteal cyst (a - transverse, b - longitudinal) and of the olecranon bursa, with the aspect of the "snowstorm" (anechoic area with hyperechoic spots). d. Gouty tophus (arrowhead), with posterior acoustic shadowing (asterisk).

be distinguished from lipoma or rheumatoid nodules which are more hypoechoic and homogenous. Features of MSU crystal deposition inside tendons and joints and even tophi (**Figure 8d**) can be detected in the setting of asymptomatic

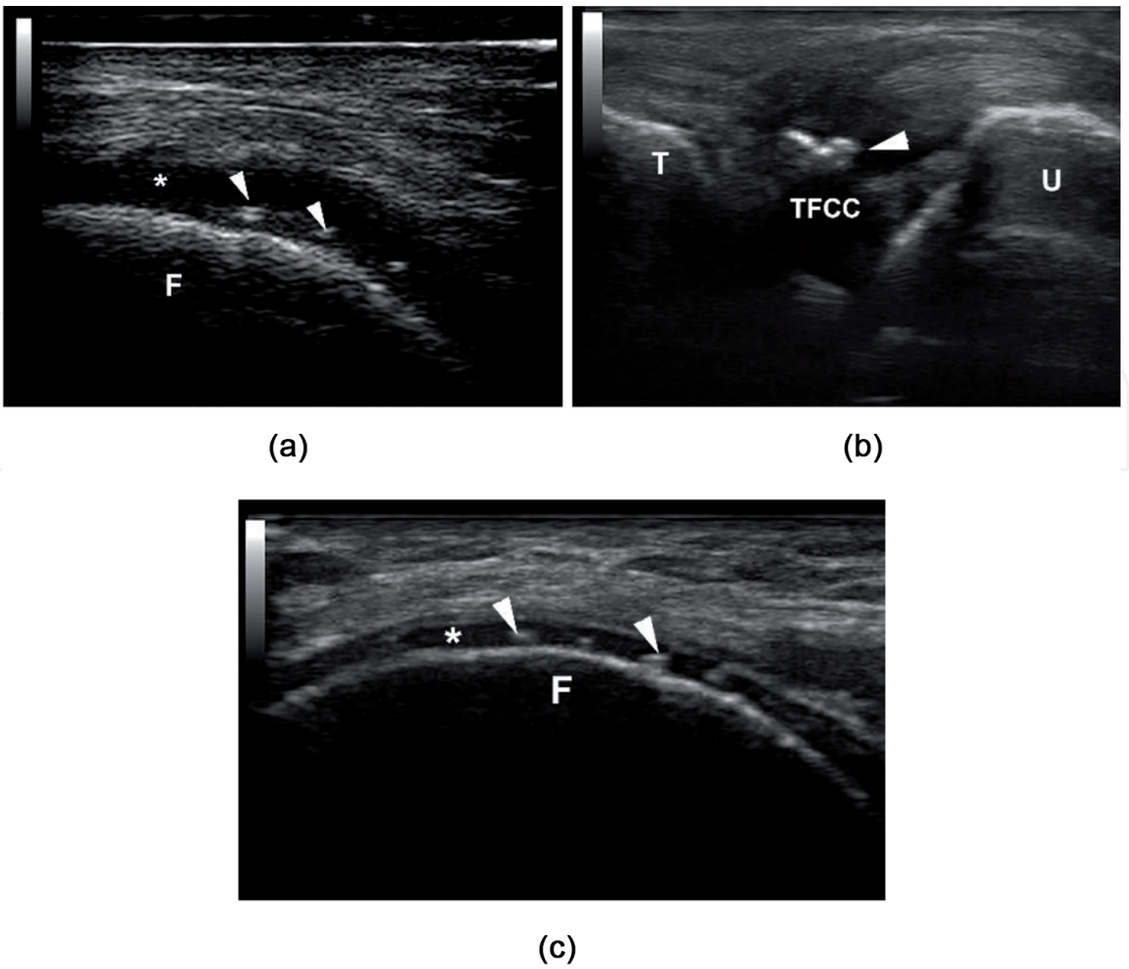


Figure 9.
Ultrasound images of calcium pyrophosphate deposits (arrowheads) in CPPD, inside the knee hyaline cartilage (a, c) and in the triangular fibrocartilage complex (b). F – Femur, TFCC - triangular fibrocartilage complex, asterisk – Hyaline cartilage.

hyperuricemia. EULAR and ACR recommendations support the use of ultrasound in gout and CPPD due to its high sensitivity and specificity [45–47]. The 2015 EULAR/ACR gout classification criteria recognize ultrasound and dual-energy computed tomography as the main imaging modalities used to accurately identify urate deposition [46].

The 2011 EULAR recommendations for calcium pyrophosphate deposition disease (CPPD) highlight the diagnostic potential of ultrasound with a high diagnosis likelihood ratio and possibly even better sensitivity than those of conventional x-rays [47]. The paper of Filippou demonstrated US to be an accurate tool for discriminating CPPD [48]. The OMERACT US group for CPPD has defined in 2017, the ultrasonographic characteristics of CPPD, in both joints and periarticular tissues [49, 50]. In contrast to gouty deposits appearance, at the surface of the cartilage, in CPPD the deposits are present inside the hyaline cartilage. The most important joints in which we can find CPPD deposits are the wrist (at the level of the triangular fibrocartilage), the knee (meniscus and hyaline cartilage) (**Figure 9**), acromioclavicular and hip joint [50].

3.4 Osteoarthritis

Features of degenerative joint disease are easily recognizable by ultrasound examination. Lesions related to osteoarthritis include varying degrees of cartilage damage and osteophyte formation. Although, conventional x-ray is also commonly used in osteoarthritis diagnosis, it can be fairly limited in earlier phases and lacks the capacity to directly visualize the articular hyaline cartilage. One of

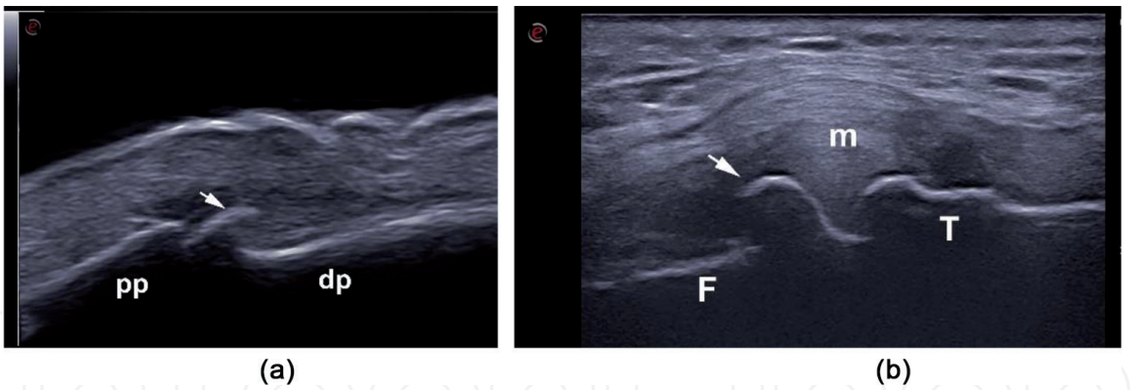


Figure 10.
Ultrasound images of step-up bony prominences, at the level of the interphalangeal (a) and femurotibial (b) joints, suggestive for osteophytes. pp – proximal phalanx, dp – distal phalanx, F – femur, T – tibia, m – meniscus, arrow - osteophyte.

the hallmarks of osteoarthritis US features is the diminished cartilage thickness. Normally, the hyaline cartilage appears as a well-defined anechoic band, due to increased water content, which lacks internal echoes [17]. US has proven to have higher sensitivity compared to conventional x-ray in the assessment of osteophytes and space narrowing. Early features of OA visible through US include: loss of the sharp contour, asymmetric thinning and changes in echogenicity of the cartilage matrix. Additionally, some forms of OA can display erosive and inflammatory changes [51]. Osteophytes are defined as step-up bony prominence seen in two perpendicular planes (**Figure 10**).

The presence of cortical bone irregularities and bony erosions can lead to difficulties in distinguishing osteophyte formations. Upon detection of osteophytes various scoring systems can be applied. This can be a simple semi-quantitative grading scale, as follows: 0 = No osteophyte, 1 = Marginal osteophyte, 2 = Medium osteophyte, 3 = Large osteophyte. Mortada and colleagues proposed a more detailed scoring system for the severity of knee osteoarthritis (see **Table 5**) [52].

The musculoskeletal US can also be applied for therapeutic purposes in degenerative diseases. Patients with OA can benefit from intra-articular infiltration with hyaluronic acid or glucocorticoid and this can be more accurately performed through ultrasound-guided injections. Besides the immediate release of synovial fluid visible during joint aspiration, inflammatory features have also proven to decrease posttreatment. Hence, ultrasound has become a useful tool in both local treatment and monitoring disease activity.

Grade 0		No osteophytes; regular end of femoral condyle without any projections.
Grade 1		Minor osteophyte; just a small projection from the femoral condyle.
Grade 2	2A	Small osteophytes; a projection from the femoral condyle that appears to have an inferior part in the joint space zone.
	2B	Large osteophyte appears to be separated from femoral condyle and to have an inferior part in joint space zone.
Grade 3		Large osteophyte appears to be separated from femoral condyle and to have an inferior part in joint space zone with small superior extension parallel to femoral bone.
Grade 4		Mainly superior osteophyte parallel to the femoral bone with or without an inferior part in joint space zone.

Table 5.
Ultrasonographic grading scale for severity of primary knee osteoarthritis by Mortada et al. [52].

3.5 Scleroderma

One of the most important clinical features of patients with systemic sclerosis (SSc) is the skin thickening. The extent of skin features in SSc is divided clinically into diffuse and limited involvement and is usually quantified using the Rodnan skin score. In addition to this, high-frequency ultrasound can also allow for a detailed assessment of skin involvement. The target measurement is the dermal thickness. For a correct assessment, the following interfaces need to be identified: surface–epidermis, epidermis–dermis and dermis–subcutis [53]. Skin features in SSc vary in time and this is detectable also through US. In the edematous phase, increased thickness associated with low echogenicity is seen due to water content. In time, fibrosis leads to increased echogenicity. Ultrasound measurements correlated well with histopathology, Rodnan skin score and EUSTAR disease activity index [5, 54]. Hongyan and colleagues defined an optimal cutoff point of 7.4 mm for skin thickness, with a sensitivity of 77.4% and specificity of 87.1% [54]. Quantitative studies of skin stiffness using sonoelastography yielded promising results. Research by Yang and colleagues indicates that Shear Wave Elastography can discriminate between SSc patients and controls (**Figure 11**), has good reliability and correlates well with skin thickness and modified Rodnan skin sore [55].

3.6 Sjögren's syndrome

Primary Sjögren's syndrome (pSS) is an autoimmune disease of the exocrine glands, which manifests mainly as hyposecretion of salivary and lacrimal glands. The diagnosis approach is generally focused on the detection of specific autoantibodies, positive ocular tests and findings of characteristic histopathological abnormalities. Sialography and scintigraphy are considered invasive and rarely used in everyday practice, while limited accessibility and the high cost of MRI also hinders its use. Studies on ultrasound have produced promising results for the assessment of major salivary glands (**Figure 12**) of pSS patients and offer a more accessible and less time-consuming alternative to other imaging tests. Still, the established

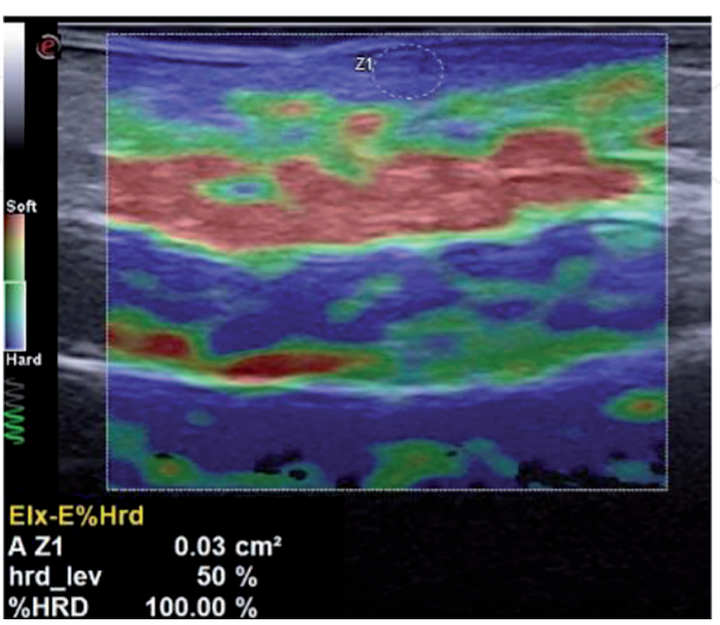


Figure 11.
Elastography of the finger volar aspect that shows the increased hardness of the epidermis and dermis, as shown by the blue color and the hardness percent.

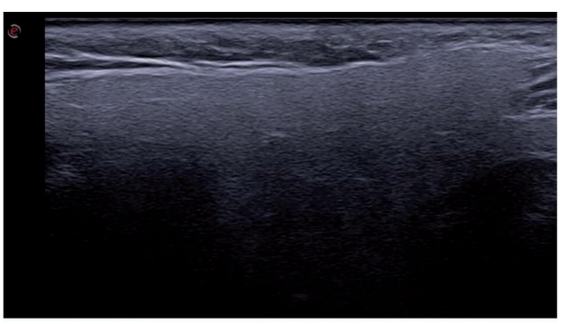
diagnostic criteria developed up until now for pSS have not included ultrasonography as a recommended diagnostic tool.

The parotid and submandibular glands can be easily examined for certain structural abnormalities, such as: parenchymal inhomogeneity, hypo-anechoic or hyperechoic areas (**Figure 12b** and **c**) (produced by cysts or calcifications), surface irregularities and changes in glandular size, intra- or periglandular lymph nodes [56].

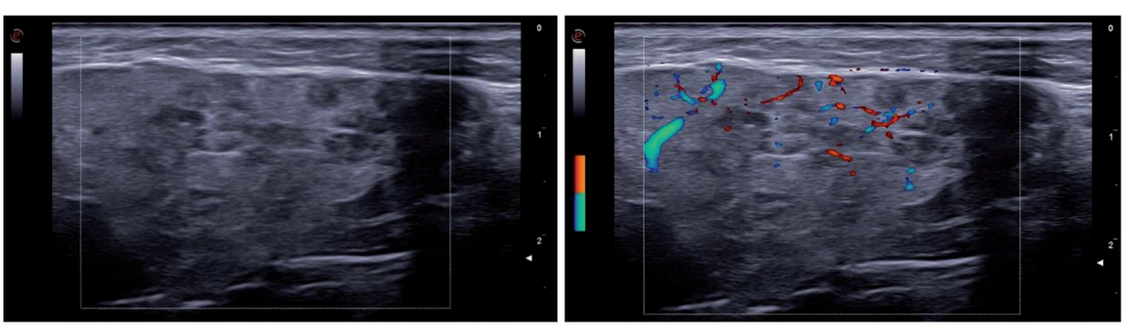
Additionally, the use of Doppler modes can identify glandular hypervascularization which has been consistently observed in pSS patients. In early phases, US is marked by an increase in glandular volume and high vascularity, while in later stages reduced volume and hypovascularization are characteristic [57]. Parenchymal inhomogeneity is the most recognizable term used in the development of numerous grading systems.

Research carried out by De Vita et al. [58], Hocevar et al. [59] and Salaffi et al. [60] provided some of the well-known semiquantitative scoring systems. All of these US scores proved high sensitivity and specificity for pSS. De Vita et al. developed a 0-3 scale for parenchymal inhomogeneity, while Hocevar et al. added 0-3 scales also for the number of hypoechogenic areas, hyperechogenic reflections and clearness of salivary gland border. Salaffi et al. proposed an extended 0-4 scale for parenchymal inhomogeneity which includes all of the features previously mentioned (see **Table 6**) [60].

Minor salivary gland biopsy remains the gold standard for diagnosis and is recommended in most patients with suspected pSS, especially in cases with positive autoantibodies. Studies evaluated the predictive value of salivary gland US for histopathology abnormalities. Miedany et al. [61] found a significant correlation between US score and histopathological score (r = 0.82). This supports the use of US when biopsy cannot be performed or in order to stratify the at-risk patients before ordering a biopsy.



(a)



(b) (c)

Figure 12.
a. Normal aspect of a parotid gland. b, c. Parotid gland US in GS (b) and PD (c) modes, with the inhomogeneous aspect, with multiple hypoechoic areas, suggestive for glandular inflammation.

Grade 0	normal US aspect of the glands
Grade 1	regular contour, small hypoechoic areas, without echogenic bands, normal or increased glandular volume (with mean values 20 + 3 mm for the parotids and 13 + 2 mm for the submandibular glands) and badly defined posterior border (definite echogenic border with respect to the neighboring structures)
Grade 2	regular contour, numerous dispersed hypoechogenic areas of variable size (<2 mm), without echogenic bands, normal or increased glandular volume and badly defined posterior border
Grade 3	irregular contour, multiple, moderate in size (2–6 mm), circumscribed or confluent hypoechogenic areas and/or multiple cysts, with echogenic bands, regular or decreased glandular volume and no visible posterior border
Grade 4	irregular contour, multiple, large (>6 mm), circumscribed or confluent hypoechogenic areas, and/or multiple cysts or multiple calcifications, with echogenic bands, resulting in severe change of the glandular architecture, decreased glandular volume and posterior glandular border not visible

Table 6.
Ultrasound semiquantitative scoring system for parenchymal inhomogeneity by Salaffi et al. [60].

3.7 Large vessel vasculitis

Ultrasound imaging can detect signs of arterial involvement in giant cell arteritis and Takayasu disease. The characteristic US features of large vessel vasculitis include the presence of a hypoechoic swollen artery wall which is surrounded by oedema, known as the halo sign (**Figure 13**).

The use of US has been studied more extensively in giant cell arteritis. Detection of the typical patchy inflammation seen in temporal arteritis can benefit greatly from ultrasound examination. Besides wall thickening, large vessel vasculitis can display lack of compressibility, stenosis and vessel occlusion [6]. Importantly, giant cell arteritis can spare the temporal arteries in some cases, and thus US examination should also include other large vessels such as the axillary or carotid arteries. The diagnostic value of US has been highlighted by its adoption in the 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ultrasound examination is included in the imaging tests used to confirm the diagnosis when large vessel vasculitis is suspected [62].

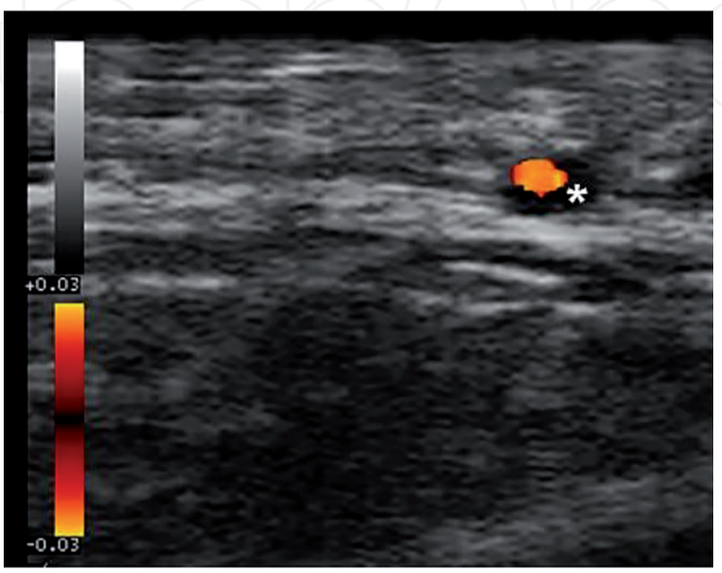


Figure 13.
Ultrasonography of the temporal artery showing a swollen hypoechoic wall – Halo sign (asterisk).

3.8 Muscular disease

Various muscle pathologies can be assessed using ultrasonography. It can detect partial and complete muscle ruptures, fluid collections, muscle infarctions or development of muscle tumors. Features of posttraumatic lesions vary by severity. Milder intensity trauma leads to interstitial hemorrhage which appears as poorly defined hyperechoic areas. In more severe trauma, an intramuscular hematoma can develop, and echogenicity will vary based on time of lesions, with a visible muscle blunt, with a "bell tongue" aspect (**Figure 14**).

On US examination, normal muscle is slightly hypoechogenic with hyperechoic septa and fascia [17]. In transverse plane, muscle tissue will normally have a "starry night appearance", while in long axis fibers run parallel to each other and at an angle towards the muscle insertion. Patients with inflammatory myopathies, such as polymyositis, dermatomyositis and inclusion body myositis, will display changes in muscle echogenicity. In acute phases, muscle edema will cause thickening and only slight increase in echogenicity which proves reversible to treatment [63]. In later

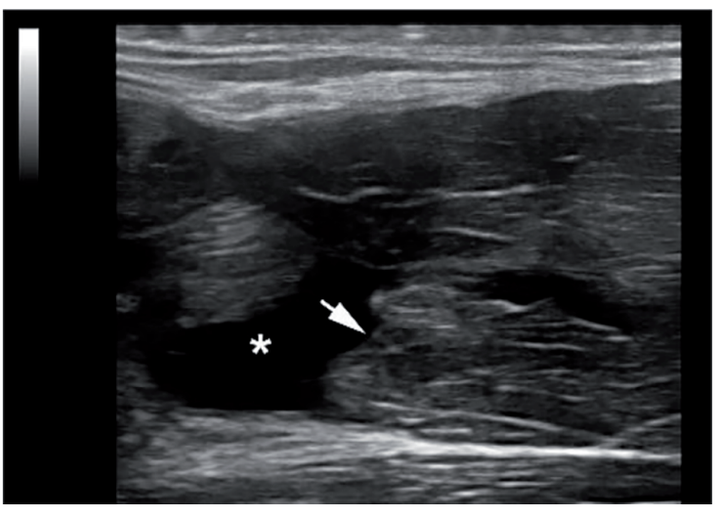


Figure 14.
Ultrasonography of the pectoralis major muscle with a lesion. Asterisk – Effusion secondary to the hemorrhage, arrow – The pectoralis muscle blunt ("bell tongue" aspect).

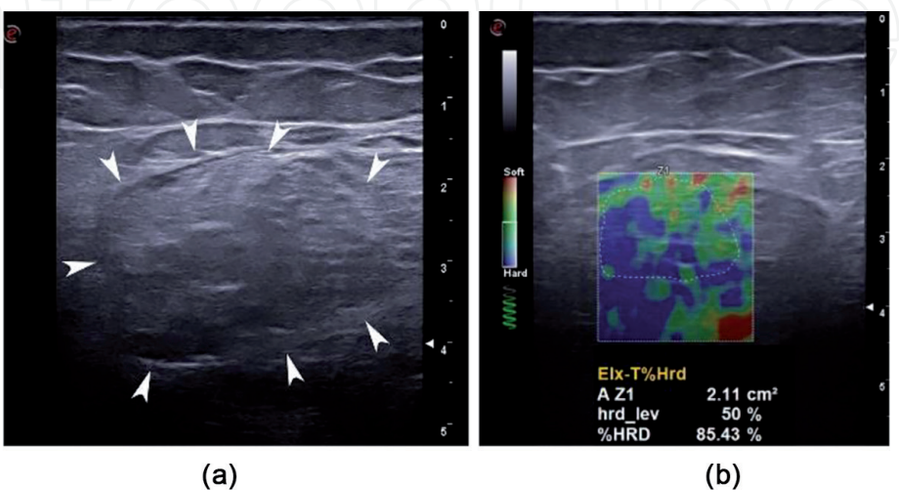


Figure 15.
Ultrasonography of the rectus femoris in a patient with polymyositis, that shows increased echogenicity and lack of the starry night appearance in GS mode (a), and decreased elasticity as showed by the blue color in elastography and the hardness percent (b).

stages, ultrasound will detect markedly increased echogenicity, muscle atrophy and reduced elasticity (**Figure 15**).

Studies have observed correlations between US and histopathology and also significant changes in muscle stiffness when applying elastographic modalities. Patients with active myositis display increased stiffness and this will be gradually reduced as more severe muscle weakness develops [64].

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