Degenerative and inflammatory musculoskeletal disorders: updates and hot topics in diagnostic and interventional imaging

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Abstract. – OBJECTIVE: The purpose of this review is to present the latest innovations and current topics in musculoskeletal diagnosis and interventional imaging, with a focus on degenerative and inflammatory diseases.

MATERIALS AND METHODS: In this study, the search was conducted through the online databases PubMed and Google Scholar, including articles published in English in the past 15 years, in order to find existing studies, clinical cases, and reviews on the latest innovations and current topics in degenerative and inflammatory musculoskeletal pathologies.

RESULTS: Imaging plays a pivotal role in the diagnosis and treatment of MSK degenerative and inflammatory disease. In the last few years continuous innovations and technological advances have allowed new clinical applications in the management of MSK disorder. Advanced magnetic resonance techniques, the introduction of fusion imaging techniques and new approaches to infiltrative medicine are revolutionizing the clinical and therapeutic approach to degenerative and inflammatory pathologies. Artificial intelligence also increasingly seeks to be applied in all fields of medicine and radiology with increasingly promising results.

CONCLUSIONS: Imaging modalities undergo continuous innovations and revolutions due to technological advances, with direct repercussions on clinical applications and new therapeutic potential through interventional radiology techniques. In recent years, there have been particular innovations in the context of musculoskeletal imaging of degenerative and inflammatory diseases, both for diagnosis and intervention.

Key Words:
Musculoskeletal imaging, Compositional MRI techniques, UHFUS, Sonoelastography, Fusion imaging, Artificial intelligence.

Introduction

In musculoskeletal medicine, multimodal imaging is a fundamental step in the diagnosis and treatment of many pathologies, including traumatic, degenerative, inflammatory and tumoral pathologies[1-12]. Imaging methods undergo continuous innovations and revolutions thanks to technological advances, with direct repercussions on clinical applications, thanks the introduction of new semiological features, the extension of diagnostic questions, increased diagnostic performance, and new therapeutic potential through interventional radiology techniques[13-20].

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In recent years, there have been particular innovations in the context of degenerative and inflammatory pathologies, both from the point of view of the diagnosis - especially for the implementation of advanced magnetic resonance techniques - and from the therapeutic point of view, for the introduction of fusion imaging techniques and new approaches to infiltrative medicine[21]. Furthermore, artificial intelligence is expanding, seeking application in all these fields[22-24]. The purpose of this review is to present the latest innovations and hot topics in musculoskeletal diagnostic and interventional imaging, with a particular focus on degenerative and inflammatory pathologies.

Materials and Methods

In this narrative review, data collection was performed through a search of the online PubMed and Google Scholar databases. We included articles published in English in the past 15 years, in order to find existing studies, clinical cases, and reviews on the latest innovations and current topics in degenerative and inflammatory musculoskeletal pathologies.

Magnetic Resonance Imaging Biomarkers in Osteoarthritis

In recent years, technological improvements have allowed imaging modalities to become increasingly essential to achieving early and accurate diagnoses in the field of rheumatic and musculoskeletal diseases[25,26].

The pathological process of osteoarthritis affects various joint structures, but the degeneration of the articular cartilage represents the "*primum movens*" in the pathogenic phases of the disease. Imaging plays an important role in the diagnosis of degenerative joint diseases, classification of severity, surveillance of progression and prediction of disease prognosis[27].

Magnetic resonance imaging (MRI), due to its excellent soft tissue contrast resolution, is the preferred imaging tool for the evaluation of different diseases affecting the musculoskeletal system, both for diagnostic and interventional purposes[28-32]. In the last years, several advanced MR imaging sequences and techniques were developed to provide a global, sensitive and specific assessment of the joint degenerative processes with semiquantitative, quantitative and compositional analysis methods[33].

Semi-quantitative MRI scoring systems are based on the global morphological evaluation of pathological changes that affect the functional and structural integrity of joints and determine the severity of the disease[34]. These scoring systems are used with standard morphological MR sequences, especially T2 and Proton Density (PD) fat-saturated sequences.

Quantitative evaluation with MRI provides a more sensitive and specific assessment of the degree of cartilaginous degeneration and is superior to semi-quantitative techniques for assessing structural changes[35,36].

MR imaging techniques are based on the modification of one or more cartilaginous ultrastructural components (e.g., glycosaminoglycans – GAG, proteoglycans – PG)[37]. These techniques include the measurement of relaxation times (T2 and T1rho mapping), the sodium imaging, the delayed gadolinium enhancement MRI of cartilage (dGEMRIC) imaging, the chemical exchange saturation transfer imaging of GAG (gagCEST) imaging and the diffusion imaging (diffusion weighted imaging – DWI and diffusion tensor imaging – DTI)[38-41].

T2 and T1ρ Mapping

These sequences measure the T1 and T2 relaxation times (expressed in ms) of the molecules present at the tissue level[42]. T2 relaxation times mainly depend on the collagen content of the extracellular matrix and the orientation of collagen fibers, and higher relaxation times are correlated with an increase in the deterioration of the cartilage matrix[43]. The relaxation time of T2 is measured as a function of the signal measured in multi-echo spin echo (SE) and fast spin echo (FSE); T2-weighted images with mono or multi-exponential decay curve at the different echo times (TE)[44]. T1ρ mapping is a compositional technique sensitive to regional changes in cartilage matrix proteoglycans characterized by a continuous resonance radiofrequency (RF) pulse. Both T1ρ and T2 mapping can be assessed both qualitatively with colorimetric scale and quantitatively by the positioning of regions of interest (ROIs).

Ultra-short time echo (UTE) T1 and T2 mapping sequences can be used to analyze tissues with low intrinsic relaxation time, such as menisci, tendons, deep layers of cartilage, and deep cartilage areas where non-UTE imaging are not sensitive enough[38] (Figure 1).

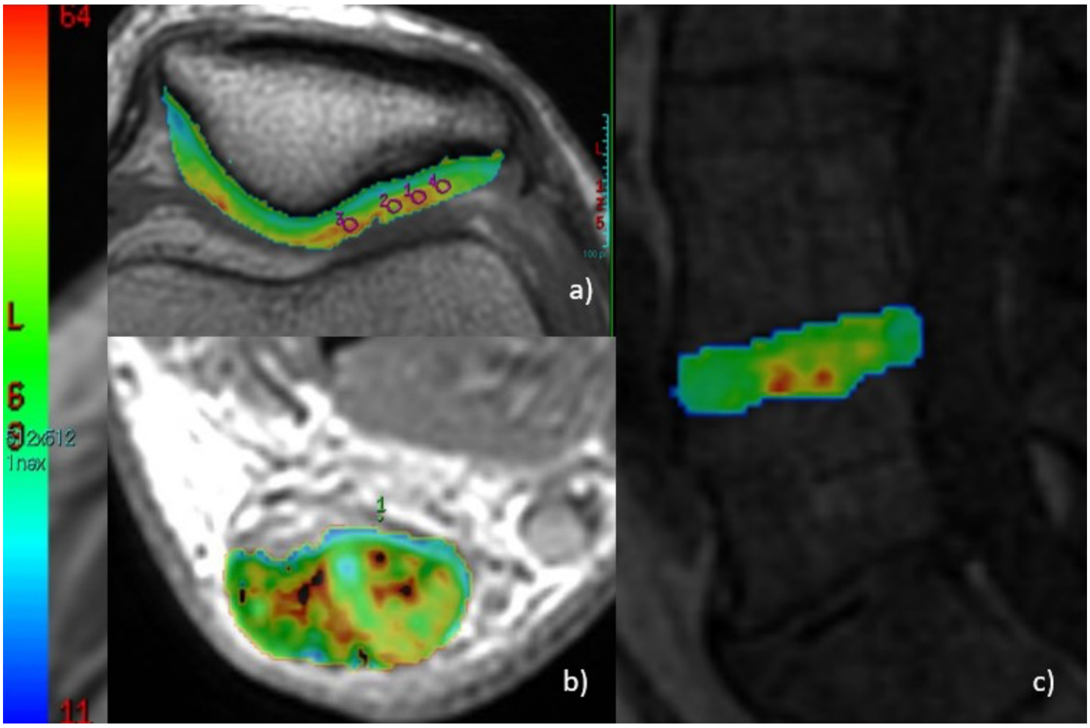

Figure 1. T2 mapping applications in musculoskeletal medicine: beyond the clinically validated application for the evaluation of articular cartilage **(a)**, T2 mapping sequences can be used to assed degenerative changes at the level of tendons **(b)**, and intervertebral disc **(c)**.

Diffusion-Weighted Imaging (DWI)

Similar to other compositional sequences, diffusion and tensor parameters correlate with the collagen and proteoglycan content within the cartilage matrix and can be used as quantitative markers of cartilage degeneration[45].

Delayed Gadolinium Enhancement MRI of Cartilage (dGEMRIC)

Gadolinium is negatively charged and is rejected by positively charged GAGs in cartilage, while in the case of cartilage matrix degradation, the amount of contrast in cartilage tissue will be increased in an inversely related manner. The dGEMRIC technique shows high sensitivity and specificity[39,45].

Chemical Exchange Saturation Transfer Imaging of GAG (gagCEST)

This sequence is based on the constant transfer of labile protons between solutes (in the case of cartilage, GAGs) and water. The proton transfer between water molecules and the one between water and GAG are different, and the difference between water-water transfer and water-GAG transfer is measured as the magnetic transfer ratio. The signal obtained from the energy transfer after radiofrequency proton saturation is proportional to the concentration of GAG in the tissue[27,46,47].

Dual-Energy and Spectral CT

The concept of spectral imaging, or dual-energy computed tomography (DECT), is an old one, described by Godfrey Hounsfield[48] in one of the first descriptions of CT in 1973[49]. The first applications of DECT to the musculoskeletal system date back to the late 1970s and early 1980s[50,51]. However, for the first commercialization of a dual-source CT we had to wait until 2006[52].

The use of two X-ray tubes with different energy levels makes it possible to extract information and characterizes the chemical composition of material, based on the different degrees of X-ray beam, absorption and attenuation, according to the atomic weight electron density of the compounds[53-55]. The ability of dual-energy CT to provide additional information regarding tissue composition, artifact reduction, and image optimization offers powerful advantages over conventional CT[56-59].

DECT has many applications in MSK imaging, especially regarding degenerative and inflammatory diseases; gout is one of the most studied diseases and on which numerous papers have been published, but DECT has also shown a potential role in the evaluation of other types of inflammatory arthritis, including septic, rheumatoid, and psoriatic arthritis.

The evaluation of gout is the most common and the most validated application of DECT in musculoskeletal imaging. The non-invasive nature of DECT makes it a promising tool in the workup of atypical presentations of gout and tracking of treatment success by quantitative volumetric measurements[60,61]. DECT is able to separate different materials, such as calcium, a high molecular weight compound, from uric acid, a low molecular weight compound, as well as cortical bone from trabecular bone. The materials are then color-coded and superimposed onto standard DECT images at a multimodality workstation, where multiplanar and three-dimensional volume rendering reformations may be produced and viewed 360° around any axis to best depict the MSU deposits[51]. DECT is an alternative modality for diagnosing gout, showing MSU crystals with a sensitivity of 78-100% and specificity of 89-100%[62,63], and nearly perfect interobserver agreement[64]. A positive DECT scan with articular or periarticular urate crystals is now part of the 2015 American College of Radiology (ACR) and European League Against Rheumatism (EULAR) classification criteria for gout[65]. DECT can be used for diagnosing pseudogout, because it reveals the presence of calcium and absence of MSU crystals[66]. The sensitivity of DECT in detecting pseudogout is lower than that for the detection of gout, but higher than that for radiographs (77.8% *vs.* 44.4%), although specificity is similar to that of conventional radiography (93.7% *vs.* 100%)[67]. DECT has a potential tool for assessing other types of inflammatory arthritis, including septic, rheumatoid, and psoriatic arthritis[68].

Iodine mapping used with dual-energy computed tomography (DECT) is an innovative image-processing technique for evaluation rheumatoid arthritis (RA) and psoriatic arthritis (PsA) of the small joints of the hands and feet[68,69]. Iodine mapping allows visualization of the iodine contrast distribution that can be displayed, by means of a color-coding, in areas where there is an abnormal accumulation of iodine contrast material, such as at the level of the synovium and pannus formation in RA and of the fibrocartilaginous entheses (synovio-entheseal complex) in PsA[68-70].

Furthermore, CT has the advantage of being able to detect structural changes due to the direct representation of the cortical bone and has been used as the gold standard instead of the histopathological reference[68]. This technique allows to detect key findings of inflammatory lesions for early diagnosis, monitoring over time and evaluation of therapeutic effect of inflammatory arthritis[68,69].

One of the most outstanding possibilities in musculoskeletal radiology is the so-called virtual non-calcium technique (VNCa technique), which makes it possible for edema to be visualized[71].

The DECT VNCa technique was introduced in 2010. Using the absorption profiles of bone mineral, yellow marrow, and red marrow over the 2 DECT X-ray spectra, this method allows for calcium subtraction through image postprocessing[72]. VNCa images can be used to evaluate osteitis in the form of bone marrow edema, correlating well with MRI ($\kappa = 0.8$)[73]. VNCa images had an excellent diagnostic performance (sensitivity, 87-93%; specificity, 94-91%; and accuracy, 90-92%) in the evaluation of the extent of bone marrow edema in sacroiliitis associated with axial spondylarthritis[74]. MR imaging remained superior for the detection of inflammatory lesions; however, DECT was more able to assess structural changes (erosion and proliferation), which was significant as proliferation is a key finding in psoriatic arthritis[75].

Artificial Intelligence (AI): from Quantitative Imaging to Radiomics

There is a growing interest in AI technology in the musculoskeletal field, as well as for oncological evaluation but also for diagnosis of fractures, osteoporosis, bone age, degenerative and inflammatory pathology[76-82]. Using a machine learning algorithm for imaging can predict the onset of osteoarthritis in healthy individuals about 3 years before symptoms or bone damage[83,84]. Quantitative evaluation is based on image acquisition and ROI segmentation. Afterwards, the machine allows to extract some characteristics, defined radiomic information. When applied in degenerative or inflammatory musculoskeletal disorders, these features are the volume and thickness of the cartilage, the strength of the signal and the bone structure[85]. Data obtained through image analysis can be combined with clinical, biological or genetic data to better guide the diagnostic-therapeutic approach[85-91]. This is "radiomics", which is based on a quantitative analysis of images and the use of these features for data mining and pattern identification, representing a fundamental starting point for the development of personalized medicine[77,92-95]. Musculoskeletal ultrasound and MRI based on AI are useful for evaluating synovitis and screening cartilage abnormalities[96]. Liu et al[97] showed that two-dimensional convolutional neural networks could achieve high sensitivities and specificities of 81 to 88% in automatic detection of femorotibial cartilage lesions. The 3D convolutional neural networks were also able to detect meniscus and patellofemoral cartilage lesions on 3D MRI data sets, with a sensitivity/specificity of 90/82% and 80/80%, respectively, compared with clinical experts. The algorithm could also categorize the severity of lesions with more than 75% precision[98]. All these studies compare the diagnostic capacity of AI algorithms to expert radiologists, who mostly provide the closest assessment to the available reality. It is possible to evaluate synovitis and characterize patients with proliferative synovial diseases such as inflammatory arthritis[99]. Using AI techniques to evaluate synovitis scores can reduce discrepancies among observers[100]. The staging of synovitis, as evidenced by the OMERACT-EULAR Synovitis Scoring (OESS) system, is useful in monitoring the activity of inflammatory arthritis, particularly rheumatoid arthritis[101,102]. Normally, the assessment of cartilage volume and thickness is carried out using artificial intelligence technology applied to MR. The cartilage evaluation is primarily performed on the knee with AI and based on thickness segmentation with quantitative cartilage measurements and image enhancement[99]. It is also possible to carry out this evaluation with ultrasound, with all the advantages related to the non - invasiveness and safety of this technique, but also the limits of the high variability randomness of AI models (e.g., different colormaps for grayscale display, dynamic range, edge enhancements, gamma correction, focal depth).

Ultra-High Frequency Ultrasound (Uhfus) and Elastography

Ultrasound (US) in musculoskeletal medicine is a first-line imaging modality, as it is non-invasive, allowing dynamic, real-time examination[103,104]. It is very useful in musculoskeletal radiology for the evaluation of small joints, muscles, tendons, ligaments, bursae, and peripheral nerves, as well as being useful for US-guided procedures[105-107]. Recently, certain technological developments have brought a good diagnostic contribution allowing a better ultrasound evaluation and characterization of tissues. US of superficial structures is performed with linear transducers with frequencies up to 18-20 MHz and provide an axial resolution of 250-500 μm[103]. Recently, the introduction of ultrahigh frequency ultrasound (UHFUS) between 30 and 100 MHz allowed an image resolution of up to 30 μm, and therefore a very fine anatomical detail[108]. Applications of UHFUS are very helpful in degenerative and rheumatic joint diseases. Wang et al[109] demonstrate that UHF probes are very accurate in detecting early osteoarthritis and identifying the rough interface of the cartilage surface, echogenicity changes, and cartilage and/or subchondral defects, with sensitivity and specificity ranges of 91-93% and 83-86%, respectively.

UHFUS is useful for assessing bone erosions, marginal osteophytes, synovitis, as well as hyaline cartilage and outcomes after different approaches to cartilage repair[110,111]. It also makes it possible to examine structures that would otherwise not be possible to examine, such as small tendons, fingers, pulleys, fascia and retinacles[105,112] (Figure 2).

The development of UHF probes has higher costs but facilitates the visualization of normal and pathological joint structures, thanks to a width of acoustic windows for the penetration of the sonographic beam[113].

Another major advance in US technology is ultrasound elastography (USE), which can assess tissue elasticity in real time[114-117]. In the field of MSK radiology, compression elastography (CE) and shear wave elastography (SWE) are the most commonly used methods[118]. The principle exploited in CE is to analyze how the tissue has a displacement after compression, shown in an elastogram, usually displayed as a color-coded image superimposed over the B-mode image[119]. In this color chart, blue usually indicates hard, red indicates soft, and green indicates a medium hard surface[120]. SWE is based on a quantitative measurement of the tissue propagation velocity distribution of the directional shear wave, produced by the US pulse. The quantitative measurement can be expressed as shear wave velocity in meters per second (m/sec) or as tissue elasticity based on shear modulus calculation in kilopascals (kPa)[118]. Elastography is useful for assessing tendinopathy and has been shown to be capable

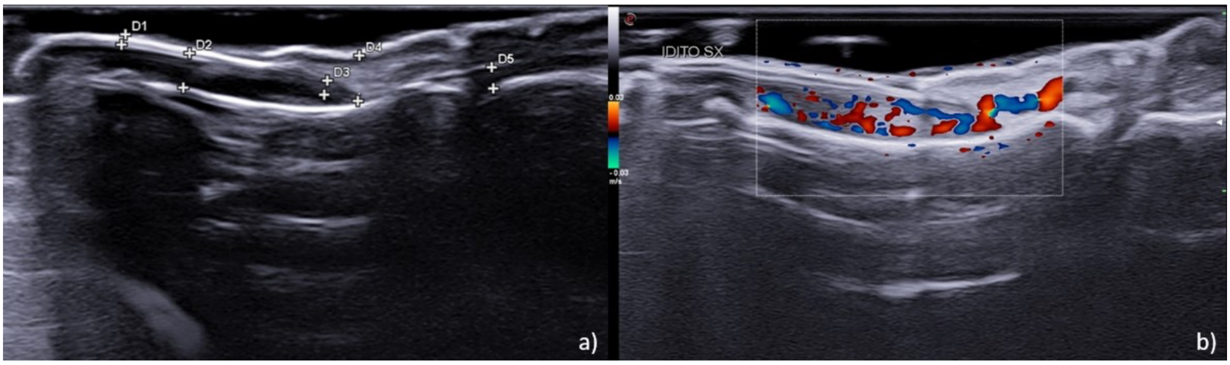

Figure 2. Evaluation of nail unit and periungual zone using UHFUS. Normal anatomy is visualized in **(a)**. In **(b)**, a case of ungueal involvement in psoriasis, charachterized by focal hyperechoic involvement of the ventral plate with fusion and irregularity of the middle and proximal third of the nail plates. There is also an increase in the thickness of the nail bed and blood flow.

of evaluating hematoma, effusion or tendon rupture, with a significant reduction in stiffness. This makes elastography especially attractive when conventional B-Mode cannot differentiate between healthy and pathological tissues[121]. Seo et al[122] reported that elastography can quantify the severity of supraspinatus muscle fat atrophy with excellent precision and inter-observatory reliability. Furthermore, according to some other preliminary results[123], elastography was found to provide a rapid assessment of early osteoarthritis, making it possible to detect changes in the elasticity of cartilage (Figure 3).

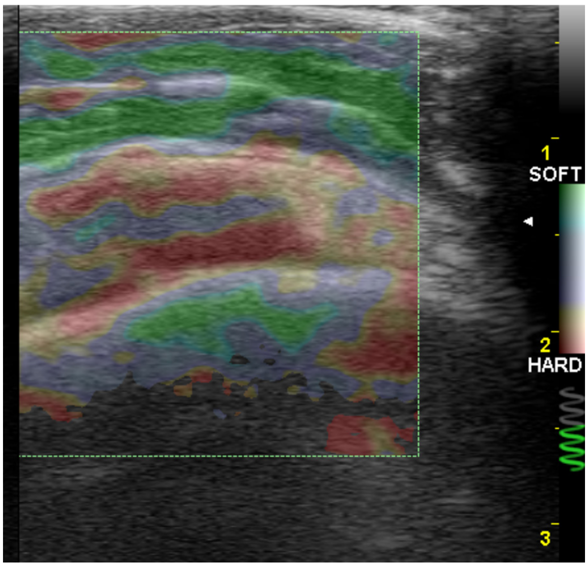

Figure 3. Assessment of supraspinatus tendon tendinoipathy using compression elastography. Harder tendon areas are displayed in red in the color-coded map, softer areas in blue-green.

Interventional Radiology: from Regenerative Medicine to Fusion Imaging

In degenerative musculoskeletal disorders, namely osteoarthritis, various treatments can be used, oral pharmacological therapy, intra-articular injections, nerve ablation or modulation, minimally invasive arthroscopic treatment and partial or total knee arthroplasty[124-126]. Among image-guided intra-articular injections, in the current practice, local corticosteroids, hyaluronic acid derivatives, platelet-rich plasma (PRP) and stem cells are mainly used. For their anti-inflammatory and immunosuppressive effects, intra-articular corticosteroids are recommended by treatment guidelines and widely used in knee osteoarthritis. The mechanism underlying the anti-inflammatory efficacy of corticosteroid is multifactorial, but generally involves blocking antigen opsonization, leukocytic cell adhesion, and cytokine diapedesis within the capillary endothelium. They have act on nuclear steroid receptors and interrupt the inflammatory-immune cascade, provide short-term moderate pain relief for up to 3-4 weeks post intra-articular injection. Corticosteroid preparations commonly used in interventional radiology are derived from prednisolone. It is possible to distinguish between hydrocortisone, which is used in periarticular treatment for its short duration of action, and the long action corticosteroids like triamcinolone or very long action like betamethasone. Intra-articular corticosteroid injections, especially when repeated, can be related to rare adverse effects comprising joint infection, tendinopathy, local nerve damage, skin atrophy, osteoporosis, increased cartilage loss and hyperglycemia, while acute complications of the technique are rare.

Hyaluronic acid (HA) acts as a joint lubricant and shock absorber, improving joint elasticity and viscosity, and it also provides nutrients to the cartilage. The primary mechanism of action is the restoration of the lubrication of the joint but although the residence time of HA inside the joint approximates 2-3 days, the effects are sustained for several weeks after HA injection.

HA binds to alloy proteins, hyaladherins, including CD44 for chondrocytes, which allows modulation of collagen by inhibiting matrix metalloproteinases (MMPs). It acts on the extracellular matrix, reducing its degeneration; it also reduces inflammation by decreasing prostaglandin (PGE2) in the synovial fluid.

HA appears effective in the treatment of arthritic pain; cross-linked products have better pain relief than linear HA. Its use is recommended for the management of osteoarthritis as a second-line treatment in symptomatic patients following conservative therapy (NSAID).

Intra-articular injection of HA (especially agents of high molecular weight) is widely used and recommended in the management of patients with knee osteoarthritis with mild to moderate clinically and radiologically confirmed disease who either had not received other therapies or in whom non-pharmacologic or pharmacologic therapies had failed or had a limited response.

Another product of regenerative medicine, platelet-rich plasma (PRP), is plasma with significantly higher platelet concentrations, together with its associated growth factors, relative to physiological plasma[127]. The platelet concentration in the PRP solution is typically 4 to 6 times the patient's baseline concentration[128].

Due to its regenerative and anti-inflammatory effects, PRP has been used for intraarticular therapy of mild to moderate osteoarthritis of the knee with favorable results. Like other regenerative medicine products, PRP has recently become known as a novel and potentially effective treatment option for osteoarthritis of the knee.

Recently, three meta-analyses have been published to support the efficacy of PRP in treating osteoarthritis of the knee. Chang et al[129], analyzed 16 studies involving 1,543 patients and found that PRP was superior to HA with respect to pain control. The beneficial effects of PRP could last up to 1 year and were more pronounced in patients with mild osteoarthritis. Steroids were shown to be effective only for one month and HA for two months.

One of the most recent products of regenerative medicine is mesenchymal/stromal stem cells (MSCs), used in the treatment of osteoarthritis[130]. Traditionally, mesenchymal stem cells are derived from autologous iliac crest samples but have been shown to be also isolated from adult (skeletal muscle, synovium, adipose tissue) and embryonic (umbilical cord) sources[131]. Mesenchymal stem cells have robust anti-inflammatory properties in that they express IL-1 Ra and can compete directly with resident macrophages of the joint space by secreting pro-inflammatory cytokines[132,133].

Recent models have demonstrated that certain growth factors, such as TGF-beta and IGF-1, can promote further remodeling of the diseased joint. The remodulation of the joints is possible thanks to the generation of natural joint environmental components of type II collagen, decorin, chondroadherin, cartilage oligomeric matrix protein, fibromodulin, aggrecan link protein, and other proteoglycans.

Ultrasound guidance in the treatment of musculoskeletal pathologies has always been indispensable to make treatment in interventional radiology accurate and safe. Fusion techniques have been recently introduced, allowing to correlate volumes and images acquired with different techniques, such as CT or MRI, in order to combine the spatial resolution of the latter with the ultrasound image, which is essential for its ease of use and feedback in real time. The main benefit of US is the expansion of clinical examination in real time, while the main benefit of MRI is the ability to visualize an intraosseous abnormality[134,135]. MRI image fusion is obtained using a navigation and positioning system that allows accurate localization of the US transducer in space with the aid of an external magnetic field generator, which is usually located close to the patient. The MR imaging sequence used in the fusion is selected by the radiologist based on the most favorable anatomic depiction of the area of interest, such as isotropic 3D for perineural injection or postcontrast sequences for detection of viable tumor for biopsy in a heterogeneous soft tissue mass[136,137] (Figure 4).

The fusion technique MR imaging-US has already been tested in a few different procedures involving the musculoskeletal system, particularly in guided biopsies and sacroiliac injections; however, the main applications of this method remain to be established[138-140].

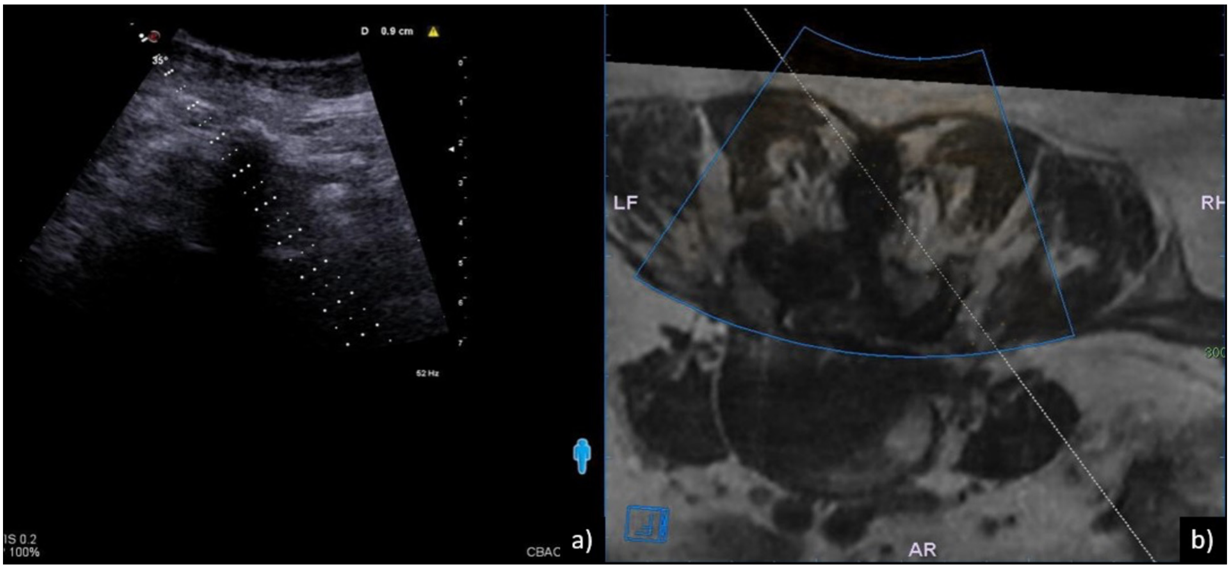

Figure 4. Fusion MRI-US image-guided lumbar spine injection. In **(a)**, the bony landmark of the spinou process is visualizaed to register the needle; in **(b)**, the MRI images are superimposed and the needle trajectory (*white line*) is displayed.

Conclusions

Imaging plays a pivotal role in the diagnosis and treatment of MSK degenerative and inflammatory disease. In the last few years continuous innovations and technological advances have allowed new clinical applications in the management of MSK disorder. Advanced magnetic resonance techniques, the introduction of fusion imaging techniques and new approaches to infiltrative medicine are revolutionizing the clinical and therapeutic approach to degenerative and inflammatory pathologies. Artificial intelligence also increasingly seeks to be applied in all fields of medicine and radiology with increasingly promising results.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Informed Consent
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Ethics Approval
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Authors' Contribution
Conceptualization; FB; Methodology: PP, FA; Data Curation: FB, Writing - Original Draft; RM, AM, GB, MPR, IS
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