



REVIEW / *Musculoskeletal imaging*

Diffusion-weighted MR imaging in musculoskeletal diseases: Current concepts



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Abstract MR imaging is currently regarded as a pivotal technique for the assessment of a variety of musculoskeletal conditions. Diffusion-weighted MR imaging (DWI) is a relatively recent sequence that provides information on the degree of cellularity of lesions. Apparent diffusion coefficient (ADC) value provides information on the movement of water molecules outside the cells. The literature contains many studies that have evaluated the role of DWI in musculoskeletal diseases. However, to date they yielded conflicting results on the use and the diagnostic capabilities of DWI in the area of musculoskeletal diseases. However, many of them have showed that DWI is a useful technique for the evaluation of the extent of the disease in a subset of musculoskeletal cancers. In terms of tissue characterization, DWI may be an adjunct to the more conventional MR imaging techniques but should be interpreted along with the signal of the lesion as observed on conventional sequences, especially in musculoskeletal cancers. Regarding the monitoring of response to therapy in cancer or inflammatory disease, the use of ADC value may represent a more reliable additional tool but must be compared to the initial ADC value of the lesions along with the knowledge of the actual therapy.

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MR imaging is currently regarded as a pivotal technique for the assessment of a variety of musculoskeletal conditions. Alongside conventional morphological MR imaging (i.e., T1-weighted, T2-weighted, STIR and T1-weighted after gadolinium administration), “functional” MR imaging has been developed to improve the diagnostic capabilities of MR imaging. Diffusion-weighted imaging (DWI) is a relatively recent MR imaging sequence that

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provides information about the degree of cellularity of lesions. The apparent diffusion coefficient (ADC) value provides information about movement of intra- and extra-cellular water.

The literature contains many studies that have evaluated the role of DWI in musculoskeletal diseases. However, to date they yielded conflicting results on the use and the diagnostic capabilities of DWI in the area of musculoskeletal diseases.

The aim of this review was to attempt to clarify the place of DWI in musculoskeletal imaging.

Principle of diffusion

The basic principle behind DWI is the stochastic Brownian motion or specific diffusion of extra-cellular water molecules within tissues [1]. Diffusivity is represented by a quantitative variable, the ADC, which is the first line assessment method for DWI data. Diffusion therefore indirectly reflects the histology of tissues (cellularity, but also fibrosis and hemoglobin degradation products) (Fig. 1).

In the case of highly cellular tissue (weak diffusion), the term restriction of diffusion is used. This is represented by

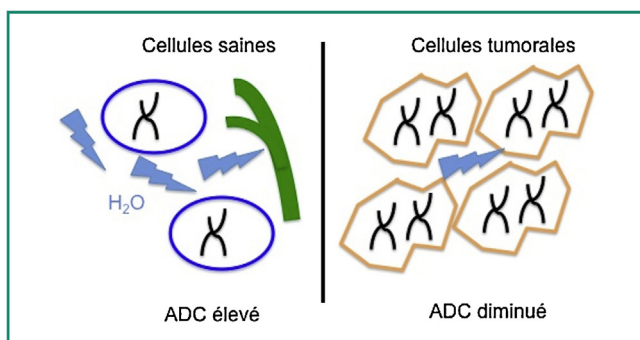


Figure 1. Low cellularity in healthy tissue and therefore straight-forward diffusion of water into the interstitial space. Conversely movement of water molecules into the interstitial is reduced in tissue with hyper-cellularity.

a large hyper-intensity on diffusion-weighted images, with a low ADC. In paucicellular tissue (high diffusion), the term increased diffusion is used and is represented by a weak hyper-intensity on diffusion-weighted MR image and a high ADC.

Malignant tissues are generally more cellular than benign tissues and extra-cellular water molecule diffusion in these tissues is therefore lower because of the presence of many macromolecules and cell membranes with anarchic cellular proliferation [1].

Technique

DWI is obtained by spin out of phase using a diffusion gradient (b) with in phase using a second gradient. When diffusion is high the return to phase is incomplete: spins are out of phase, move and no longer make use of the back in phase gradient. The signal is therefore reduced on DWI and the ADC is raised. In lesions with high cellularity, diffusion is restricted: the spins are out of phase and poorly mobile and return to phase. The signal is maximal in diffusion-weighted imaging (in the case of cytotoxic oxygen) and the ADC is low.

Several b factors (b values) may be chosen. The use of b factors varies but is generally high. If $b=0$ or low, a T2-weighted image is obtained without a true diffusion-weighted image. Conversely if the b value is high (for example $b=1000$) a genuine diffusion-weighted image is obtained beyond the T2 and perfusion image, generally with poorer spatial resolution and a poorer signal to noise ratio (SNR) (Fig. 2). Diffusion-weighted MR images must therefore be assessed visually, comparing the images obtained with a low b value (T2-weighting) to those obtained with a high b value. The difference in signal between these two images is related to water diffusion. This type of analysis is highly subjective and poorly reproducible.

ADC analysis is the first line assessment method for diffusion data. The ADC is visible in grey shades or in color (via a look up table) on the ADC map of a lesion and is expressed quantitatively as $\text{mm}^2 \cdot \text{s}^{-1}$. A minimum, mean or maximum

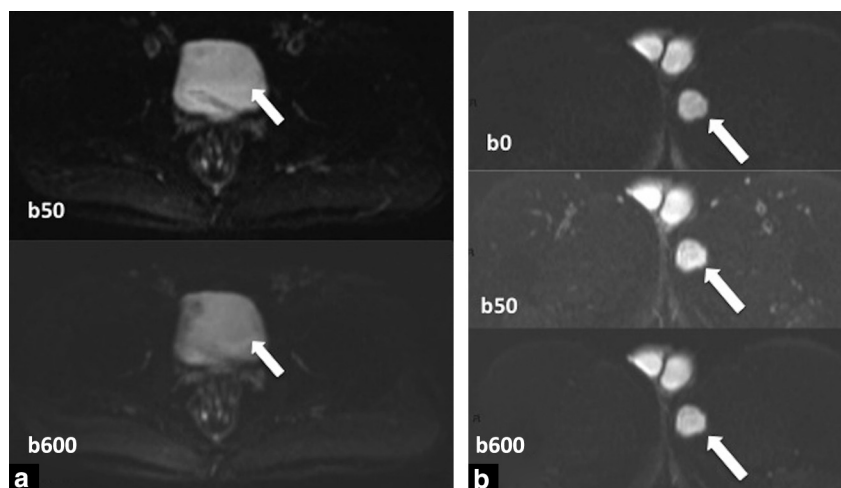


Figure 2. Illustration of image depending on the b value chosen with a liquid hyper-intensity on diffusion-weighted imaging of the bladder (a) which falls progressively and a tissue hyper-intensity on diffusion-weighted imaging of the tumor (b): in a 25-year-old patient which persists when the b value increases (arrows).

ADC can be calculated but it is usually the mean ADC that is used despite the fact that the minimum ADC value better correlates with histological findings [2–4] (Fig. 3).

Alongside the b factor in DWI, there are several types of sequences used, each of them having its own advantages and limitations [3].

Five types of DWI sequence can be distinguished:

- spin echo DWI: this is a simple spin echo sequence which has the advantage of being a homogeneous sequence with a high SNR but with the detriment of a long acquisition time;
- SS-EPI (Steady-State Echo planar): this is a fast spin echo sequence with planar echo (impulse couple of 90 and then 180 degrees) on T2-weighting. The SNR and image acquisition time are satisfactory although large magnetic susceptibility artefacts may occur. This is the imaging sequence which is most often used, in our experience (Fig. 4);
- MS-EPI (MultiShot Echo planar) is also an echo planar and is less sensitive to artefacts and distortion effects, increasing spatial resolution but at the penalty of a longer image acquisition time;
- SS-FSE (Single Shot Fast Spin Echo) (rare or haste) is a fast spin echo “single shot” T2-weighted MR sequence. The acquisition time and spatial resolution are identical although it has the advantage of multiple images being acquired;
- SS-FP DWI (Steady-State Free Precession): this is an echo gradient imaging sequence with fat saturation. The b values are low enabling a qualitative analysis.

One should note that usually musculoskeletal lesions are assessed using an SS-EPI with a high b value (over 600).

The “T2 shine through” should be understood. This is, conventionally, an intense diffusion-weighted image without a reduction in the ADC (no restriction) because of

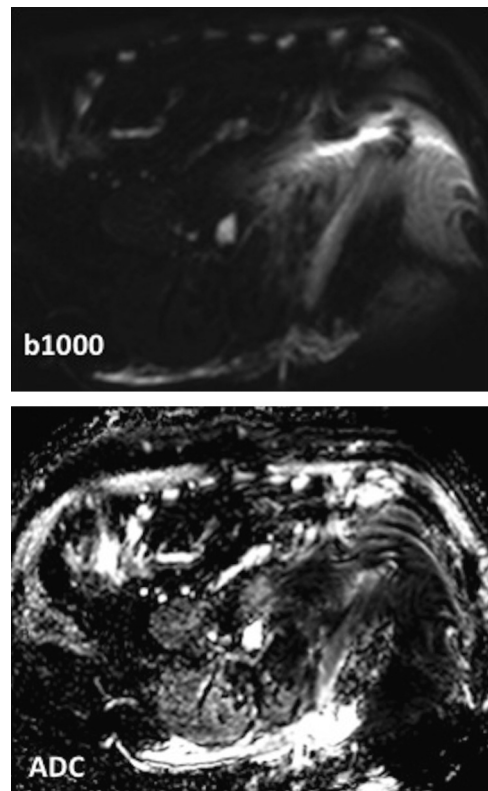


Figure 4. Seventy-nine-year-old woman with hip prosthesis. Magnetic susceptibility artifact on DWI is due to the prosthesis.

the presence of large amounts of fluid in the lesion. Any diffusion-weighted imaging must, therefore, be interpreted by a comparison against conventional T1- and T2-weighted anatomical images, possibly using gadolinium enhanced T1-weighted imaging [4] (Fig. 5).

All possible interpretations of DWI are summarized in Fig. 6 [3].

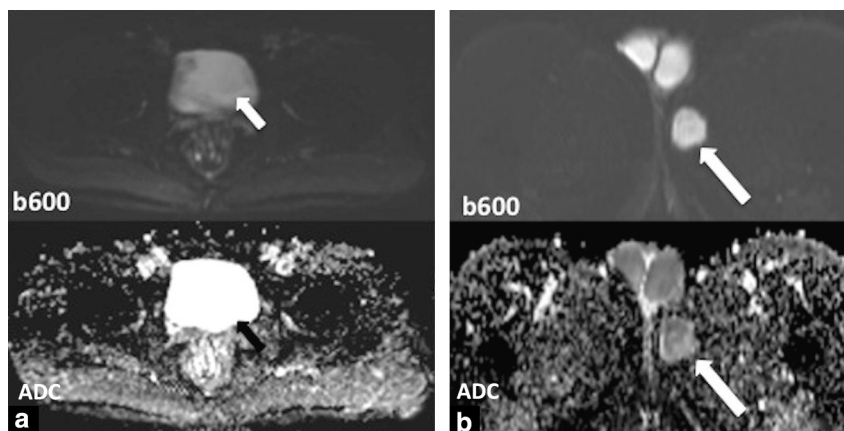


Figure 3. Twenty-five-year-old male. DWI shows moderate hypersignal of the bladder with a b value of 600 (white arrow in a) with no restriction of diffusion and a high ADC (black arrow in figure a) compared to a soft tissue tumor (in a) also with a hyper-intensity on $b600$ DWI with restricted diffusion and a low ADC (white arrows in figure b).

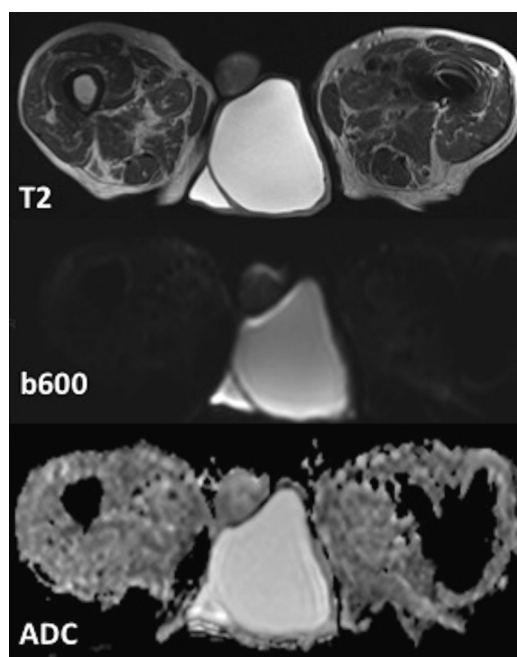


Figure 5. Forty-three-year-old male with left hydrocele. DWI shows T2 “shine through” effect. Note the hyper-intensity on b600 T2-weighted images with no reduction in the ADC.

Clinical applications

Oncology

Primary bone tumors

Early studies dealing with DWI were intended to characterize bone tumors and attempted to distinguish between malignant and benign tumors [3].

Basically, it is widely accepted that, in malignant aggressive tumors the ADC is low, whereas it is high in benign tumors. Things are more complicated than this, however,

and far less black and white. The actual question is to determine the most discriminating threshold value because of overlap in ADC values between benign and malignant tumors.

A large number of studies have yielded conflicting results and have found different cut off ADC values although the most discriminating ADC value appears to be near $1 \times 10^{-3} \text{ mm}^2 \cdot \text{s}^{-1}$.

According to Neubauer et al., a mean ADC value $\leq 1.03 \times 10^{-3} \text{ mm}^2 \cdot \text{s}^{-1}$ is a strong indicator of a primary malignant tumor. Ginat et al. combined this mean ADC value with a value of $1.65 \times 10^{-3} \text{ mm}^2 \cdot \text{s}^{-1}$ for a benign tumor [5,6].

The major difficulty is that all of these studies are difficult to compare because of variations in histological types of tumors, differences in DWI techniques (equipment, b values and DWI sequences). All authors, however, agree upon the fact that an aggressive tumor has a very low ADC (Figs. 7 and 8).

In addition to the problem of the most discriminating cut off value to differentiate between benign and malignant tumors, there is a problem distinguishing between tumors along the same histological continuum. Ginat et al. found an overlap in ADC values between an extensive chondroma as compared to a low grade chondrosarcoma. DWI also fails in eosinophilic granulomas because of their high cell density [6].

One should note that at present no cut off value has been validated as a consensus in the literature in order to distinguish between benign and malignant tumor and that DWI of any primary bone tumor should be interpreted according to its matrix and therefore its appearance on standard MR imaging (T1- and T2-weighted MR images and T1-weighted after gadolinium administration).

After attempting to characterize a tissue, DWI was then used for monitoring bone tumors on treatment.

The assessment of the response of osteosarcoma and Ewing's sarcoma to chemotherapy appears to conform well, with an increasing ADC from baseline when the tumor shows good response to therapy [7,8]. Its use in the follow-up of treated tumors appears to be less problematic than in the initial characterization of the lesion as variations in ADC value are interpreted by comparison with the initial ADC value [9] (Fig. 9).

Khoo et al. found the minimum ADC to be useful in follow up, the differences being more significant than for the mean ADC value, particularly in osteosarcomas [3]. They also highlighted the problem of interpreting DWI if partial or total necrosis was present with the appearance of “T2 shine through” effect which can be a major diagnostic pitfall [4].

Take home point

The increase in ADC value from pre-treatment baseline correlates with a good response to treatment.

Intensité du signal avec b>600	ADC	Interprétation
↗	↘	Hypercellarité: tumeur +++, abcès, produits de dégradation du sang
↗	↗	T2-Shine through, nécrose
↘	↗	Liquide, nécrose, tumeur glandulaire
↘	↘	Tumeur fibromusculaire, graisse
↘	↔	Tumeur fibreuse pauvre en eau
↗	↔	T2-Shine through

Figure 6. Table shows interpretation according to the raised b signal and ADC on DWI (modified from Khoo et al.).

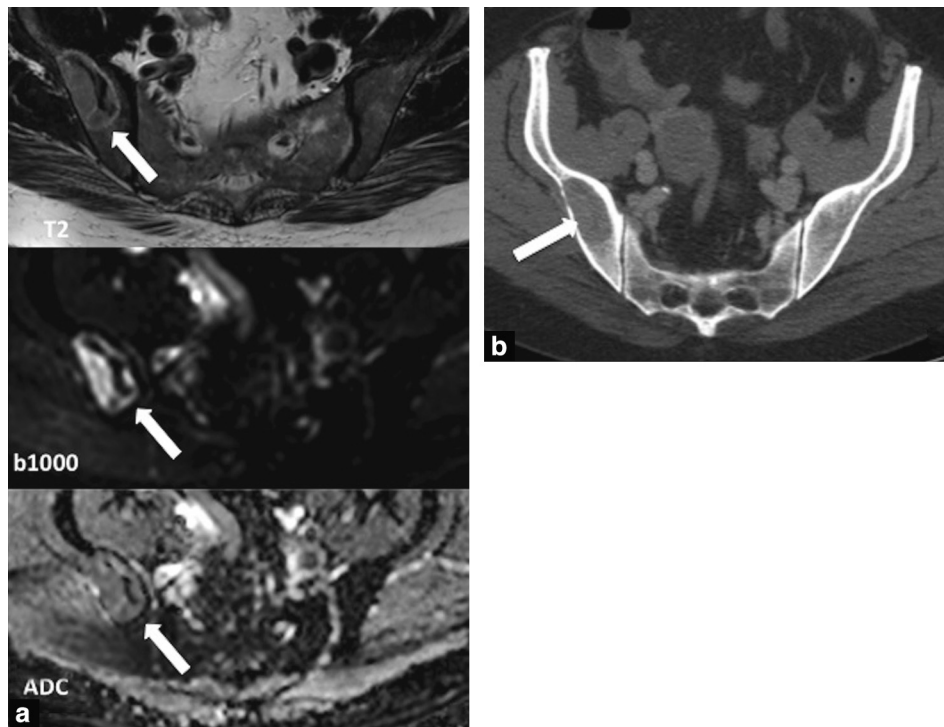


Figure 7. Sixty-six-year-old female with a past history of ovarian cancer. Found to have an osteolytic lesion in her right iliac wing (arrows). A CT-guided biopsy with histological examination revealed a plasmacytoma of the right iliac wing (arrows). Note the b1000 hyper-intensity and reduced ADC (a). Corresponding CT (b).

Soft tissue tumors

Following the same principle as for bone tumors, DWI in soft tissue tumors has been assessed in order to distinguish malignant from benign lesion, with a significantly lower ADC in malignant lesions.

Interpretation of the diffusion-weighted image must take account of the composition and heterogeneity of the tumor (cartilage, myxoid matrix, fibrosis fat, blood). The ADC is higher in cartilaginous and cystic myxoid tissue. DWI must therefore be interpreted along with conventional anatomical images (T1- and T2-weighted and T1-weighted after gadolinium administration) (Figs. 10, 11, 12).

According to Nagata et al., DWI helps discriminate between myxoid and non-myxoid tumor and between benign non-myxoid and malignant non-myxoid tumor [10]. Genovese et al. showed that benign myxoid tumors can also be distinguished from malignant myxoid ones whereas Maeda et al. did not reach similar conclusions [11,12].

Oka et al. reported that diffusion helped distinguishing desmoid tumor from malignant tumor and according to both Drapé and Oka et al., DWI is also useful to differentiate sarcomas with internal bleeding from space-occupying chronic hematomas [4,13].

As for bone tumors, several studies have reported different “cut off” ADC values. Razek et al. defined a cut off ADC value of $1.34 \text{ mm}^2 \cdot \text{s}^{-1}$ in tumors of the extremity with accuracy, sensitivity and specificity of 91%, 94% and 88%, respectively for discriminating between benign and poorly differentiated tumors [14]. Nagata et al. defined a cut off of $1.35 \text{ mm}^2 \cdot \text{s}^{-1}$ in aggressive tumors compared with

$1.97 \text{ mm}^2 \cdot \text{s}^{-1}$ in benign lesions and Van Rijswijk et al. found ADC values of $1.08 \text{ mm}^2 \cdot \text{s}^{-1}$ and $1.71 \text{ mm}^2 \cdot \text{s}^{-1}$ [15,16].

DWI appears to perform well in the assessment of response to chemotherapy of soft tissue sarcomas with an increasing ADC from baseline in good responses [17,18].

Take home point

At present no cut off point has been established in the literature as a consensus to distinguish a benign from a malignant tumor and any soft tissue tumor must be interpreted alongside its appearance on conventional images and its matrix.

Oncologic staging assessment

Several studies have evaluated the capabilities of DWI for the detection of secondary lesions from solid cancers and lymphomas [19]. DWI provides complete mapping of tissues and therefore local, regional and remote “staging” of the disease.

Whole body MR imaging with DWI images can be used for full screening (bone and lymph nodes) and is superior to other imaging techniques (i.e., scintigraphy, computed tomography (CT) or PET-CT) in prostatic cancer (Fig. 13). It is also effective for the follow-up of patients after treatment. In general, there is a gradual increase in the ADC value and a drop in signal intensity due to cellular apoptosis in

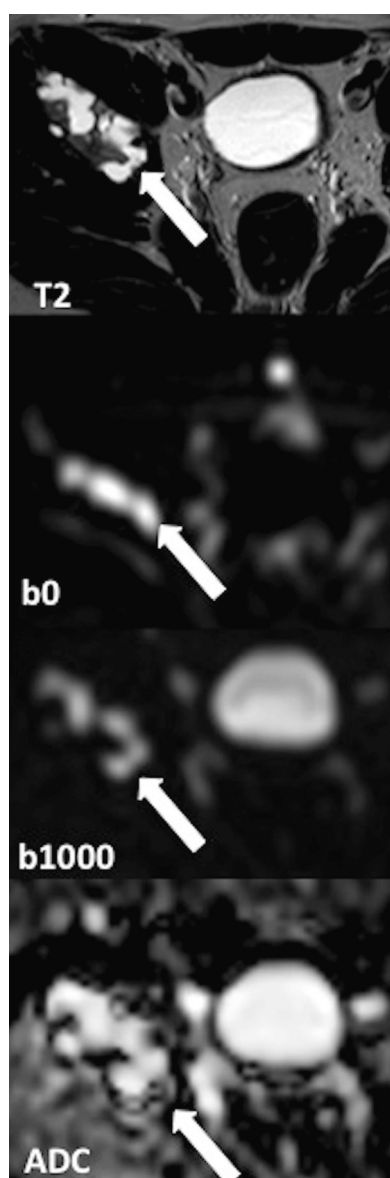


Figure 8. Fourteen-year-old male was found incidentally in a radiological assessment of right hip pain to have a cystic lesion in the right iliac wing suggestive of an aneurysmal cyst (arrow). Note the typical appearance on $b1000$ T2-weighted hyper-intensity with no reduction in diffusion.

tumors that respond favorably to treatment, although these changes are often slow and heterogeneous [20,21].

DWI has been found to be more sensitive than scintigraphy and PET-CT in children and young adults for the evaluation of bone metastases, Ewing's sarcoma or osteosarcoma despite a number of false positive findings due to hyperplastic bone marrow as a result of the use of granulocyte growth factors [3] (Fig. 14).

Myeloma is a malignant condition, which has been widely studied both for detection and follow-up (Fig. 15). Despite inconsistent results particularly in terms of reproducibility, three different studies have demonstrated that DWI has an undisputed role in monitoring response to treatment [22–24]. However Messiou et al. found that the combination of T1-weighted and STIR images is still superior to DWI [25].

Lin et al. reported that DWI is a useful technique to depict diffuse bone marrow involvement in lymphomas, as it shows a drop in ADC value [26,27].

Take home point

“Whole body DWI” used in combination with standard MR images provide complete mapping in the initial assessment of the disease and are useful for the follow-up of the disease after treatment.

Inflammatory rheumatic diseases

Seronegative spondyloarthropathies

In the field of seronegative spondyloarthropathy, DWI has inferior diagnostic capabilities than STIR MR imaging but is equivalent to contrast-enhanced MR imaging to detect the lesion [28].

In order to distinguish between rheumatic and degenerative disease, Bozeyik et al. and Dallaudière et al. showed substantial differences in ADC values (greater ADC value in rheumatic disease) between sacro-iliac and spinal disease, with a cut off value around $0.57 \text{ mm}^2 \cdot \text{s}^{-1}$. These results should be confirmed by larger studies [29,30] (Fig. 16).

Many studies have shown that DWI is a useful technique for the follow-up after treatment because the ADC drops in patients respond well [31].

Rheumatoid arthritis

The use of DWI in rheumatoid arthritis has received little attention in the literature [32]. Two studies have studied inflammation of the synovial C1 C2 pannus [33,34]. They both concluded that DWI has little utility in everyday practice [33,34].

Take home point

ADC may be of diagnostic assistance if difficulties arise in distinguishing between degenerative and rheumatic disease. ADC value is generally higher in inflammatory disease.

Infectious disease

Diffusivity is restricted in osteomyelitis, spondylodiscitis or in abscesses containing a viscous liquid, which is protein rich. The large increase in diffusivity and drop in ADC value therefore make it difficult to distinguish between malignant and infectious lesions (sensitivity and specificity around 60%) (Fig. 17) [3].

DWI appears to be useful to distinguish degenerative disease from infection, the ADC value being higher in bone marrow infection (Fig. 18) [35].

Take home point

Unlike cerebral imaging, diffusion-weighted imaging does not appear to be useful in soft tissue abscesses.

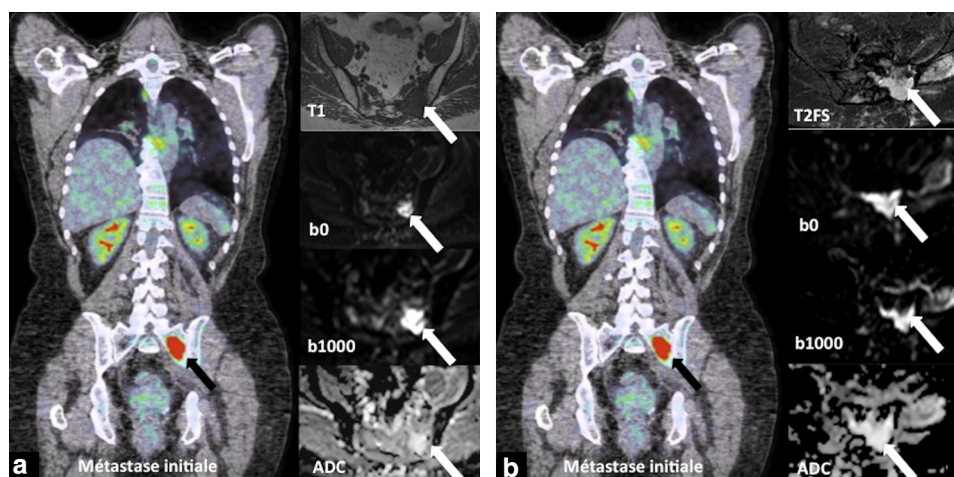


Figure 9. (a) fifty-one-year-old male followed up for lung adenocarcinoma treated by right upper lobectomy. The patient developed left sciatica due to a left sacral secondary site. Note the relative restriction of diffusion with a slightly reduced ADC (arrows). (b) same patient after radiotherapy and then surgery because of persistent pain. Note the b1000 hyper-intensity with no restriction of diffusion indicating early post-surgical changes (sero-sanguinous liquid) (arrows).

Degenerative disease

DWI imaging has been used to study bone in order to define normal values of around $0.45 \text{ mm}^2 \cdot \text{s}^{-1}$ (Fig. 19) [30,36]. DWI findings correlate with the findings observed on T1-weighted and STIR MR images and with bone densitometry [37].

Griffith et al. found that quantification of osteoporosis correlated with microperfusion abnormalities but not with the diffusion itself [38].

Some authors tried to quantify DWI of disc degeneration. They found a reduced ADC value when active disease was present and therefore disc dehydration, although this is not used in daily practice [39]. However the ADC value of bone marrow appears to be increased in degenerative disease compared to normal cancellous bone [30] (Fig. 20).

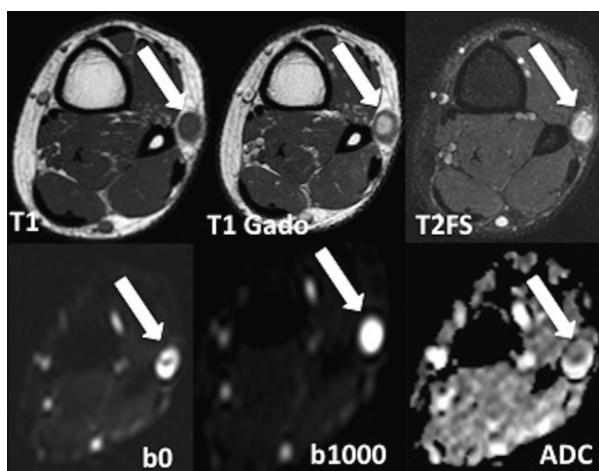


Figure 10. Forty-year-old male with pain in the left superficial fibular nerve territory with a trigger area. MRI reveals a schwannoma of the leg along the tract of the nerve. Note the central restriction of diffusion (arrows). The imaging diagnosis is made from conventional image sequences.

Trauma

As part of the investigation, DWI appears to be useful in trauma and for the post-operative examination of the tibial tunnel after anterior cruciate ligament reconstruction. ADC falls compared to post-gadolinium enhanced MRI (as does enhancement) if the response to surgery is good although this is still only a single feasibility study [40,41].

Take home point

DWI is currently only being assessed in degenerative and traumatic disease.

A benign vertebral collapse is due to microfractures with edema. In malignant collapse fracture, fracture is combined with involvement by malignant cells (Fig. 21). Qualitatively, abnormal persisting hyper-intensity on DWI after 6 months is suggestive of a pathological collapse fracture [3,42]. Quantitatively, ADC value is significantly lower in a malignant collapse fracture with a sensitivity of 100% and specificity 93%. Furthermore, DWI is similar to T1-weighted, T2-weighted and STIR MR imaging in terms of lesion characterization (Fig. 22) [42]. No definite cut off ADC value however has been found; the ADC value strongly depends on the extent of tumor infiltration in the vertebra, which may vary greatly according to the stage of the disease [43,44].

In a recent series, Pozzi et al. also found similar results, whereas Geith et al. found that DWI was not specific enough to characterize a collapse fracture [45,46]. These inconsistent results should be confirmed by larger prospective trials.

All authors agree that DWI must be interpreted with the knowledge of the type of lesion (sclerotic, lytic or mixed, metastases, etc.), the treatment (radiotherapy, chemotherapy, bisphosphonates) and knowledge of the possible T2-weighted “shine through” effect, in order to avoid interpretation errors.

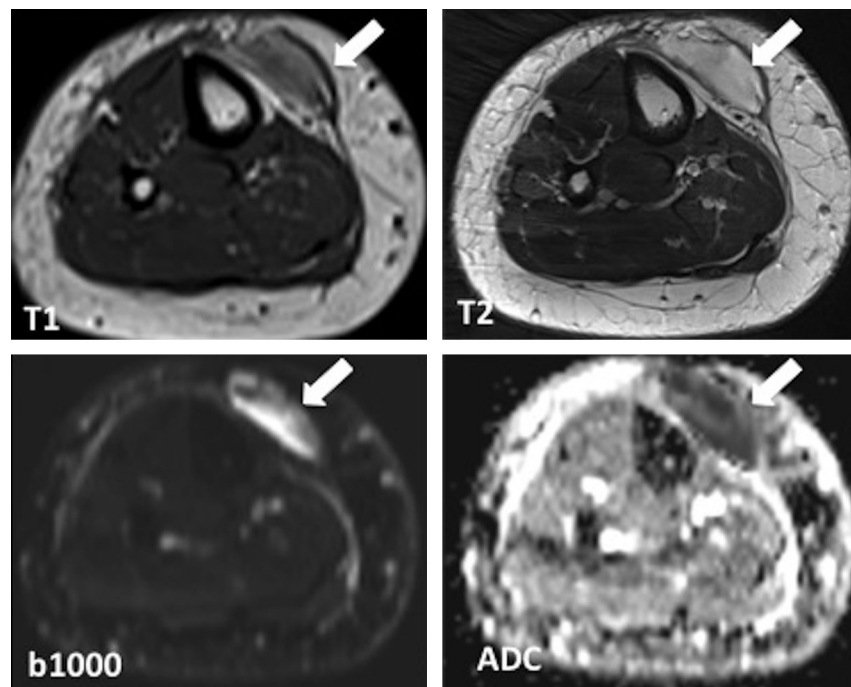


Figure 11. Thirty-eight-year-old woman with sub-acute hypodermic hematoma of the leg due to direct injury. Note the restriction of diffusion with a reduced ADC (arrows).

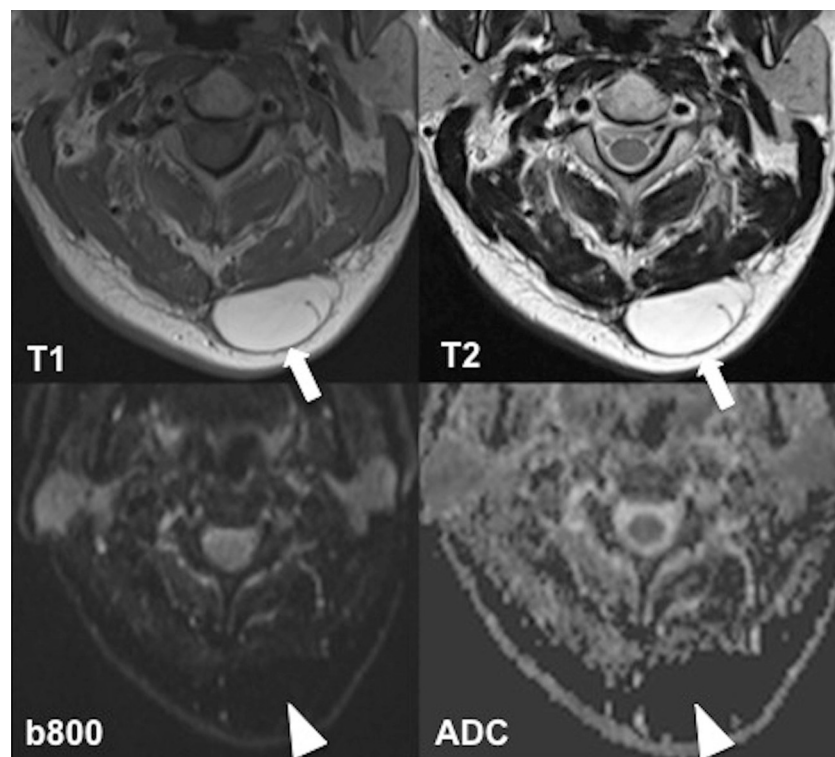


Figure 12. Fifty-three-year-old man with superficial neck lipoma. The lesion shows hyper-intensity on T1- and T2-weighted MR images (arrows) with a very low diffusion and ADC values (arrow heads).

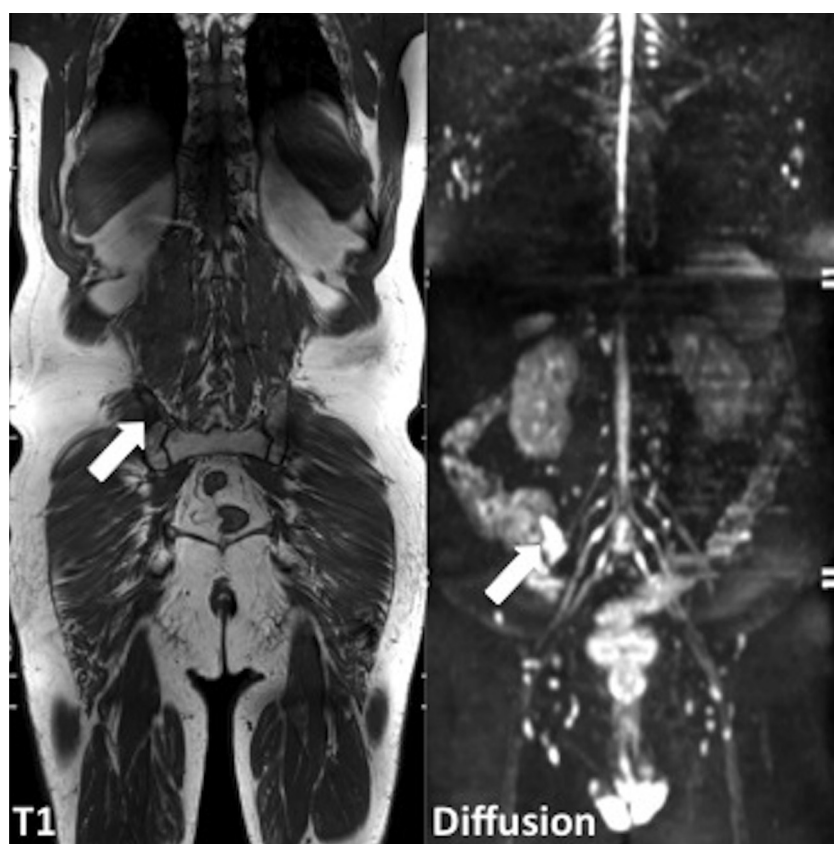


Figure 13. Seventy-two-year-old man with prostatic adenocarcinoma. Staging is performed using whole body MRI. Note the restriction of diffusion from a right iliac metastasis (arrow).

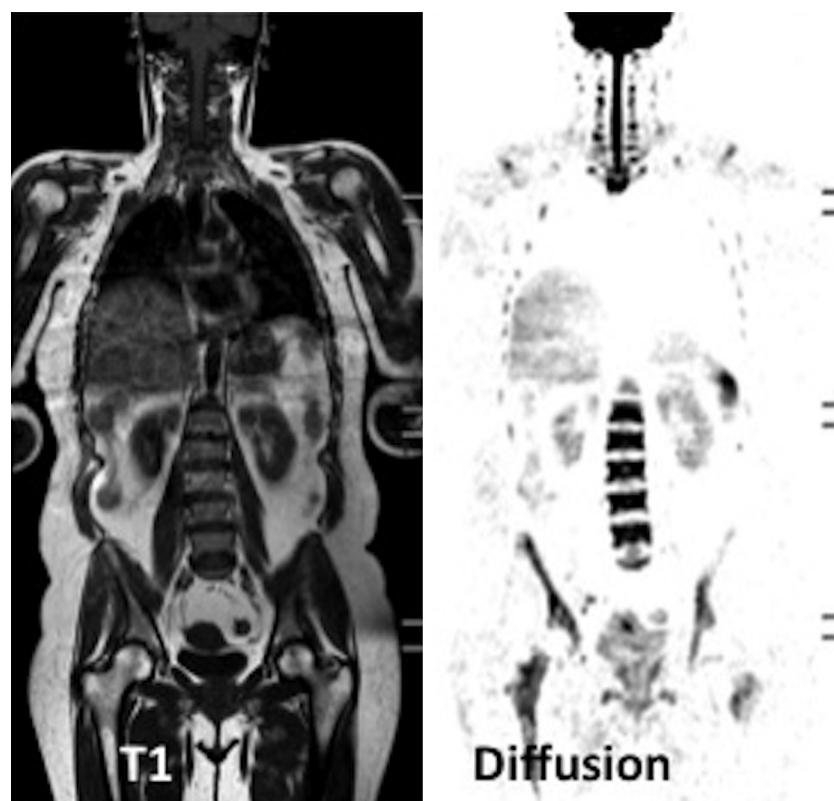


Figure 14. Stimulated bone marrow in a fifty-five-year-old male patient treated for lung malignancy. Note the DWI hypo-intensity (in the negative: "PET-like" or "scinti-like") and the appearance of the bone marrow on T1-weighted imaging.



Figure 15. Multiple myeloma with diffuse infiltration of the bone marrow. Note the DWI hypo-intensity (in the negative: “PET-like” or “scinti-like”) with a T1-weighted hypo-intensity and a slight STIR hyper-intensity in a fifty-six-year-old woman (arrows).

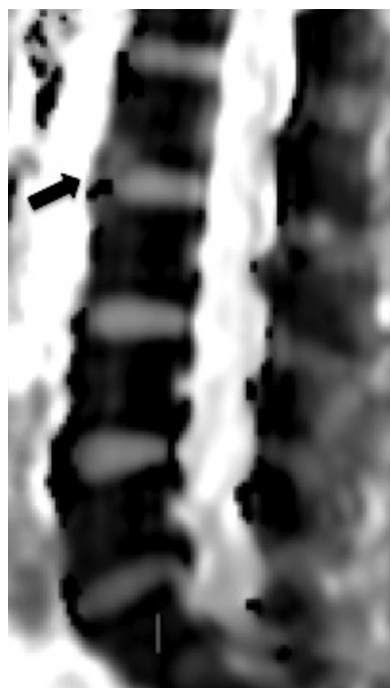


Figure 16. ADC mapping, 35-year-old male with Romanus spondylitis (arrow).

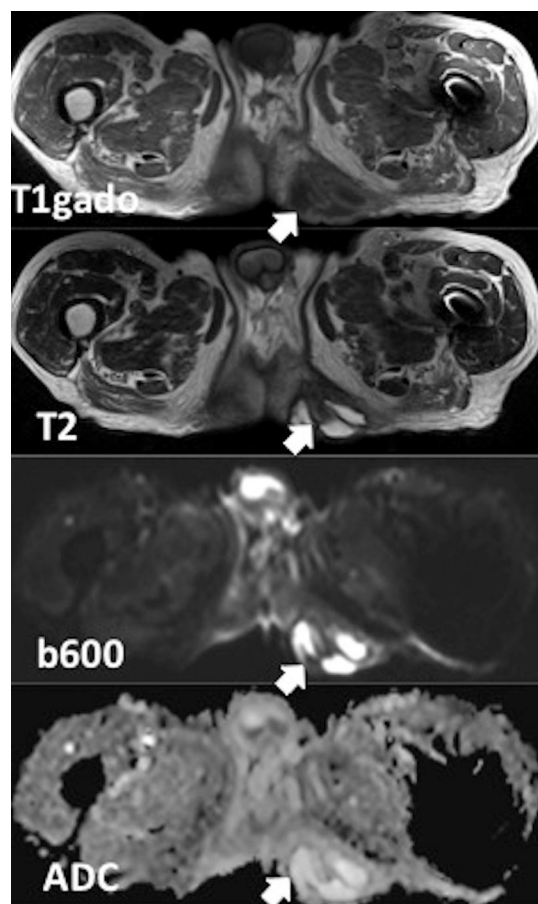


Figure 17. Eighty-two-year-old male patient with a left buttock abscess. Note the restriction of diffusion with a moderately reduced ADC associated with a thick purulent liquid component (arrows).

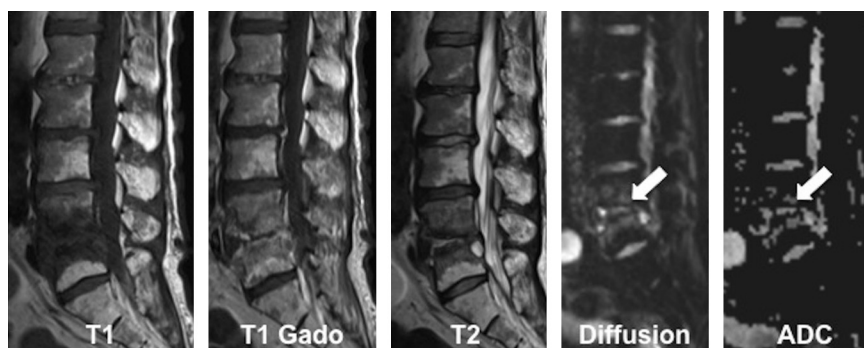


Figure 18. Sixty-eight-year-old male with pyogenic L4-L5 spondylodiscitis. Restriction of diffusion from the disc is due to pus which is rich in cells (arrows).

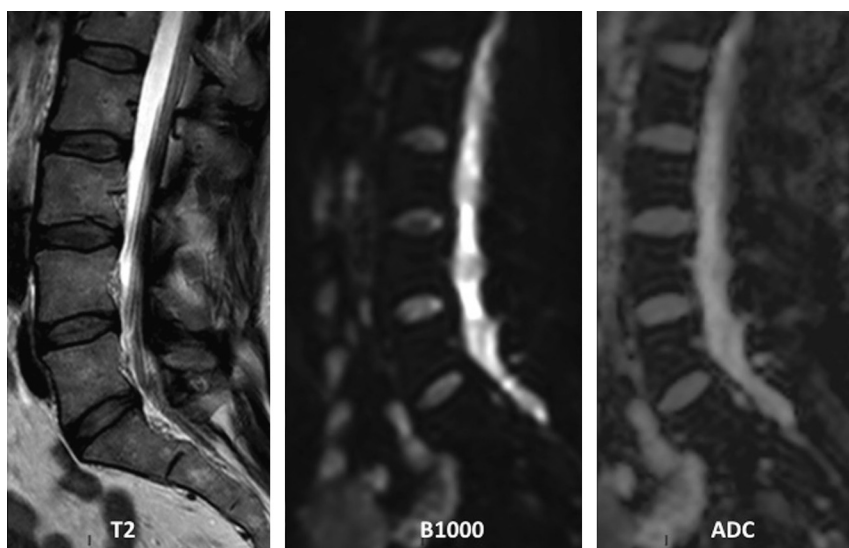


Figure 19. Thirty-three-year-old man with normal spine.

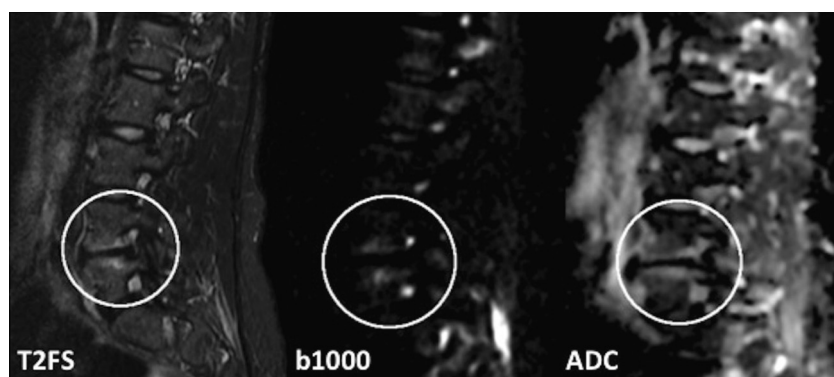


Figure 20. Sixty-five-year-old woman with Modic type 1 inflammatory changes in L4-L5 disc disease. Note the increase in diffusion compared to healthy bone.

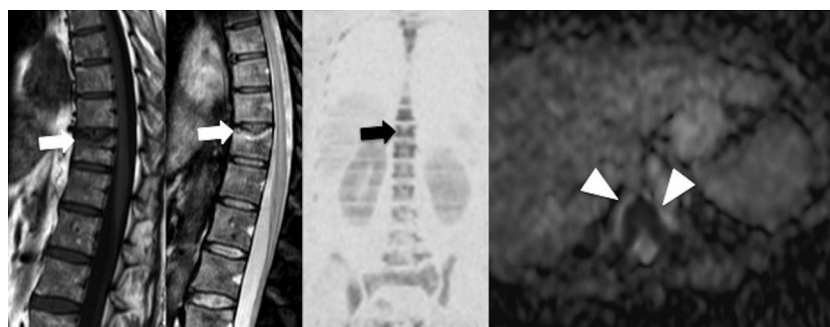


Figure 21. Sixty-six-year-old woman with benign collapse fracture of T11 (white arrows). Note the absence of restriction of diffusion in the vertebra (black arrow) and peri-vertebral soft tissues (arrow heads).

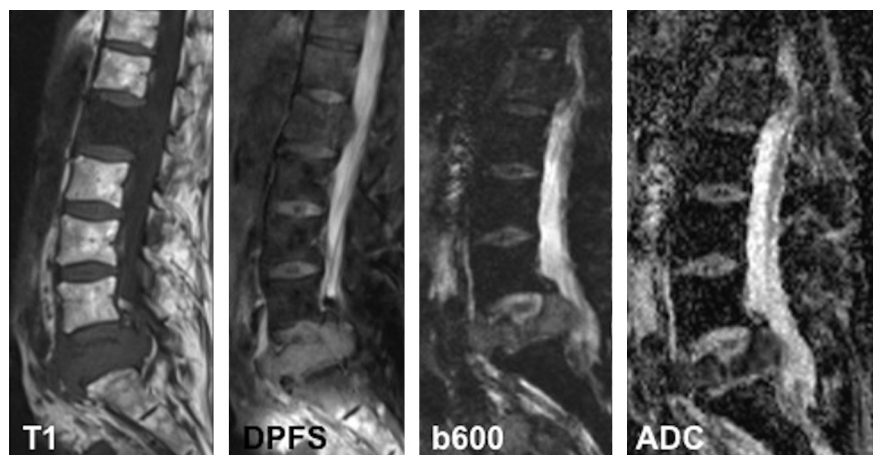


Figure 22. Sixty-six-year-old man with gastric adenocarcinoma presenting with malignant collapse fracture of L5. Note the *b600* hyperintensity with pronounced drop in ADC value.

Take home point

No definite threshold ADC value has been established to differentiate between benign and malignant collapse fracture and any lesion must be interpreted according to the clinical situation (time between the collapse and pain) whether or not the collapse is sclerotic in appearance and the treatment the patient is receiving.

which extent the use of normalized ADC might help improve lesion characterization in musculoskeletal diseases [47,48].

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Conclusion

DWI is a very sensitive technique that is currently used in a large number of musculoskeletal conditions. DWI is a valid technique for the staging of some solid cancers. In terms of tissue characterization, DWI should be regarded as a diagnostic aid and DWI features must always be compared to the appearances of the lesion on conventional MR imaging particularly in oncological disease. In terms of follow-up of cancer or rheumatic diseases, the change in ADC values may provide additional evidence of response to treatment, which is more reliable than the initial characterization of a lesion but still must be interpreted compared to the initial ADC value of the lesion and knowledge of actual treatments. Finally, in light of recent studies regarding the use of normalized ADC, further studies should be done to determine to

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