Editorial

The relevance of T2 relaxation time in interpreting MRI apparent diffusion coefficient (ADC) map for musculoskeletal structures

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Random movement ("molecular diffusion") of particles comes from the thermal energy that they possess at any given temperature above absolute zero. A self-diffusion coefficient of around 2.3×10^{-3} mm^2/s has been demonstrated earlier by a sample that contains small molecules, for example, water, at approximately 25 ℃ (room temperature) (1). This motion of water molecules can be hampered by the presence of cell membranes and macromolecules, and the *in vivo* organ apparent diffusion coefficients (ADCs) measured by magnetic resonance imaging (MRI) are expected to be smaller than *in vitro* water phantom value. On the other hand, *in vivo* organ ADC is also contributed by tissue perfusion. In body water, such as the case of gallbladder, ADC is measured to be around 3×10^{-3} mm^2/s (2), which is affected by the body temperature, composition of bile fluid, as well as the body bulk motion due to respiration and cardiovascular pulsating, etc.

ADC values of some *in vitro* phantom results, *in vivo* muscle, cartilage, intervertebral disc NP and IAF (nucleus pulposus and inner annulus fibrosus) (3), and bone marrow are listed in *Table 1* (4-20). Liver, the largest solid organ in the body, has an ADC of around 1.07×10^{-3} mm^2/s (6), and also considering free water has an *in vitro* ADC of around 2.2×10^{-3} mm^2/s (4,6), we intuitively feel that the ADCs of cartilage (around 1.5×10^{-3} mm^2/s) and disc NP and IAF (around 1.9×10^{-3} mm^2/s) are 'unrealistically high'. Compared with the liver ADC of 1.07×10^{-3} mm^2/s and spleen ADC of 0.8×10^{-3} mm^2/s (6), muscle ADC, being around 1.55×10^{-3} mm^2/s, also appears to be high. Recently, Wáng *et al.* (21-25) proposed that *in vivo* ADC measure is strongly associated with T2 relaxation time (T2 time) [*Table 2*, *Figure 1* (26-44)]. Wáng *et al.* (24) divide T2 time into short T2 time band (<60 ms), intermediate T2 time band (60–80 ms), and long T2 time band (>80 ms, all 3 T values). For the short T2 time band, there is a negative correlation between T2 time and ADC. For the long T2 time band, there is a positive correlation between T2 time and ADC. A tissue likely measures a low ADC if its T2 time is close to 70 ms. The phenomenon shown in *Figure 1* can help explain the counterintuitive ADC values commonly seen in a number of musculoskeletal tissues.

In experimental studies, it was suggested that the hepatic blood volume including that of the large vessels is about 25 mL/100 g, whereas this value is 3 mL/100 g in skeletal muscle (45). Though we would think that the ADC of muscles will not be higher than that of liver with the liver more richly perfused by hepatic artery and portal vein and with lots of sinusoids and space of Disse, however, muscles

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Table 1 A list of ADC values of some phantoms, muscle, cartilage, intervertebral disc NP and IAF, and bone marrow

Authors	Materials/tissues	Mean ADC ($\times 10^{-3}$ mm^2/s)	Magnet[#]	b value (s/mm^2)[§§]
Kalaitzakis *et al.* (4)	Water phantom	2.20	1.5 T	0–1,500, 10 b values
Kalaitzakis *et al.* (4)	5% sucrose solution phantom	1.88	1.5 T	0–1,500, 10 b values
Gatidis *et al.* (5)	Water phantom	2.15	3.0 T	0–1,000, 10 b values
Gatidis *et al.* (5)	Polyethylene glycol (10 mM) phantom	1.86	3.0 T	0–1,000, 10 b values
Kim *et al.* (6)	Liver[##]	1.07	3.0 T	0, 800
Kim *et al.* (6)	Spleen	0.79	3.0 T	0, 800
Sandberg *et al*. (7)	Muscles (11.2 years)[¶]	1.48	3.0 T	50, 600
Chen *et al.* (8)	Paraspinal muscle (57.0 years)[¶]	1.55	3.0 T	50, 800
Padhani *et al.* (9)	Psoas muscle[¶]	1.39	1.5 T	50, 800 (or 900)
Raya *et al*. (10)	Muscle (review)[¶]	1.60	3.0 T	
Zbýň *et al*. (11)	Knee articular cartilage	1.90	3.0 T	50, 500, 100
Ukai *et al.* (12)	Knee articular cartilage (51.5 years)	1.40	3.0 T	0, 600
Raya *et al.* (10)	Articular cartilage (review)	1.50	3.0 T	
Hamaguchi *et al.* (13)	Disc NP and IAF (33.4 years)[¶¶]	1.78	3.0 T	0, 1,000
Shen *et al.* (14)	Disc NP and IAF (24.3 years)[¶¶]	1.99	1.5 T	0, 800
Niu *et al.* (15)	Non-degenerated NP and IAF (20–29 years)	2.16	1.5 T	0, 500
Niinimäki *et al*. (16)	Non-degenerated NP (49 years)	1.65	1.5 T	0, 500
Sandberg *et al.* (7)	Red bone marrow (11.2 years)[§]	0.86	3.0 T	50, 600
Padhani *et al.* (9)	Red bone marrow[§]	0.68	3.0 T	50, 800 (or 900)
Zbýň *et al.* (11)	Bone marrow (knee)[§]	0.53	3.0T	50, 500, 100
Padhani *et al.* (9)	Yellow bone marrow[§]	0.38	1.5 T	50, 800 (or 900)
Byun *et al.* (17)	Sacrum yellow bone marrow (70 years)[§]	0.21	1.5 T	0, 650
Raya *et al.* (10)	Bone marrow (review)[§]	0.45	3.0 T	–

[#], it is generally considered that diffusion is *per se* not a nuclear magnetic resonance phenomenon. Magnetic field strength should have little impact on ADC values measured (18,19); [##], older age is commonly associated with higher liver iron content and higher fat content, both can lead to lower ADC measure (20); [¶], muscle fascia contain fat. In a defined muscle region, fat portion in the fascia may increase in older subjects, and this leads to lower muscle ADC measure; [¶¶], discs of mixed degeneration grading; [§], bone marrow ADC depends on the ratio of red marrow to yellow marrow. The data of Sandberg *et al.* (7) may be closer to pure red marrow ADC; [§§], ADC measure is affected by b value selection during data acquisition and the noise levels, however, besides muscle, perfusion contribution to ADC is small for most of the skeletal tissues. ADC, apparent diffusion coefficient; NP, nucleus pulposus; IAF, inner annulus fibrosus.

have a shorter T2 time than the liver (*Table 2*). In the study of Wall *et al*. (26), muscle measured an ADC of 29 ms whereas liver measured an ADC of 45 ms at 0.35 T. In the study of de Bazelaire *et al.* (27), muscle measured an ADC of 29 ms whereas liver measured an ADC of 46 ms at 1.5 T. The phenomenon as demonstrated in *Figure 1* shows, with liver data as the reference, the shorter T2 time of muscles is associated with an increased ADC value for the muscle (relative to the liver). *Figure 1* also helps to explain that cartilage and disc NP and IAF measure very high ADC not because these tissues have true high tissue diffusivity, but instead because of their T2 times being both away from the intermediate T2 time band of 60–80 ms (at 3 T). Moreover, cartilage and disc NP and IAF demonstrate high ADC due to the opposite reasons, with cartilage having a relatively short T2 time and non-degenerated disc NP and IAF

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Table 2 A list of T2 time values of some musculoskeletal structure and disorders and tumors of the body and brain

Authors	Tissues	Mean T2 (ms)	Magnet[#] (T)
Wall *et al*. (26)	Liver	45	0.35
de Bazelaire *et al*. (27)	Liver (31.5 years)	34[¶]	3.0
de Bazelaire *et al*. (27)	Liver (31.5 years)	46	1.5
Bogaert *et al.* (28)	Liver (47.1 years)	46	1.5
Wall *et al*. (26)	Muscle	29	0.35
de Bazelaire *et al*. (27)	Paravertebral muscle (31.5 years)	29	3
Lang *et al*. (29)	Leg muscle in rat	33	2.0
Pettersson *et al.* (30)	Muscle	32	0.15
Gold *et al.* (31)	Muscle (27–38 years)	32	3.0
Gold *et al.* (31)	Muscle (27–38 years)	35	1.5
Raya *et al*. (10)	Muscle (review)	32	3.0
Gold *et al.* (31)	Knee articular cartilage (27–38 years)	37	3
Gold *et al.* (31)	Knee articular cartilage (27–38 years)	42	1.5
Roth *et al*. (32)	Knee articular cartilage (16 years)	38	3.0
Ukai *et al.* (12)	Knee articular cartilage (51.5 years)	40	3.0
Ruiz Santiago *et al*. (33)	Patellar cartilage (16–45 years)	41	1.5
Raya *et al*. (10)	Articular cartilage (review)	37	3.0
Niu *et al.* (15)	Non-degenerated discs NP and IAF (20–29 years)	164	1.5
Wang *et al.* (34)	Non-degenerated discs NP and IAF (32 years)	130	3.0
Yang *et al.* (35)	Non-degenerated discs NP and IAF (44 years)	138	3.0
Stelzeneder *et al.* (36)	Non-degenerated discs NP (19 years)	238	3.0
Bouhsina *et al*. (37)	Non-degenerated discs NP and IAF in dog	249	1.5
Wall *et al*. (26)	Abscess various body sites	81	0.35
Pettersson *et al.* (30)	Chondrosarcoma	120	0.15
Pettersson *et al.* (30)	Malignant fibrous histiocytoma	92	0.15
Pettersson *et al.* (30)	Osteogenic sarcoma	75	0.15
Lang *et al.* (29)	Osteogenic sarcoma—rat model	73	2.0
Arita *et al*. (38)	Active prostate cancer bone metastasis	82	3.0
Jung *et al.* (39)	Breast cancer	90	3.0
Baohong *et al.* (40)	Parotid gland cancer	97	3.0
Hepp *et al*. (41)	Prostate cancer	80	3.0
Gu *et al.* (42)	Grade II glioma	164	3.0
Gu *et al.* (42)	High-grade glioma	127	3.0
Oh *et al*. (43)	Gliomas	160	1.5
Oh *et al*. (43)	Meningiomas/metastases	125	1.5

Data from tumors of the body and brain represent a few random selections for illustration only. [#], there is a notion that T2 time does not change much over the range of field strengths used for routine clinical MR imaging (0.2 to 3.0 T) (44); [¶], the value of 34 ms for liver at 3.0 T is likely underestimated, i.e., liver T2 time at 3.0 T may be longer. NP, nucleus pulposus; IAF, inner annulus fibrosus; MR, magnetic resonance.

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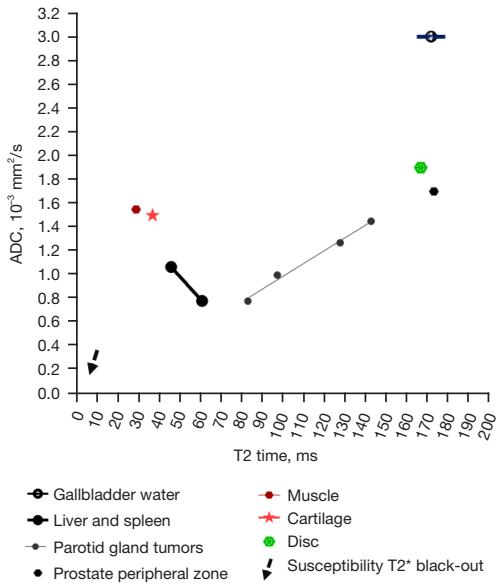

Figure 1 Relationship between T2 time and ADC at 3 T. The graph is initially from Wáng and Ma (24). Data sources for liver, spleen, parotid gland tumors, and prostate also see Wáng and Ma (24). T2 time for the liver is assumed to be 42 ms (*Table 2*). Data points for muscle, cartilage, and intervertebral disc are newly added (values based on *Tables 1*,*2*). There are large variations for reported intervertebral disc T2 time and ADC values, thus mean values for the discs are presented simplistically (the data from dog not counted). For data with T2 time <60 ms, there is a negative correlation between T2 time and ADC. For data with T2 time >80 ms, there is a positive correlation between T2 time and ADC. Dotted arrow denotes susceptibility T2* black-out, which is observed with structures having a very short intrinsic T2 signal due to very short T2*. In this graph, dotted arrow is for illustration only, and does not reflect true quantitative values for susceptibility T2* black-out. ADC, apparent diffusion coefficient.

having a long T2 time (*Table 2*).

A few musculoskeletal lesions also demonstrate unusual ADC values. Pyogenic abscess fluid (i.e., pus) tends to demonstrate a very low ADC (e.g., 0.63×10^{-3} mm^2/s) regardless of the location of the abscess (46-49). It is counterintuitive that abscess pus, being fluid or semi-fluid, has a very low ADC measure. Recently Wáng noted that (25), abscess pus having a T2 time of about half that of body water (around 80 ms) contributes to very low ADC measured by MRI [*Figure 1*, *Table 3* (9,17,41,43,48-59)]. Abscess pus may not have truly restricted diffusion compared with many other *in vivo* solid tissues. Morán *et al.* (50) and Einarsdóttir *et al.* (51) reported myxoma ADC values of 2.38×10^{-3} and 2.80×10^{-3} mm^2/s respectively, which are quite high. Quantitative data on T2 time for musculoskeletal myxoid remain limited, however, it is known that myxoid substance has a long T2 time (as noted with bright signal on T2 weighted images). Myxoma has a high ADC likely due to myxoid substance's long T2 time. Another disease type is chondrosarcoma. Chondrosarcoma has a long T2 time (e.g., 120 ms) and high ADC measure [e.g., 2.3×10^{-3} mm^2, *Table 3* (53)]. It is unlikely that chondrosarcoma has a true high tissue diffusivity. T2 shine-through refers to high signal on diffusion weighted images that is not due to restricted diffusion, but rather to long T2 time in some tissue or body fluid (52). It is considered that this T2 shine-through error can be avoided with assessment of the high b value images and the corresponding ADC map. The ADC map is considered to have corrected the T2 shine-through (52). Thus, the ADC measure of lesions such as myxoma cannot be explained by the T2 shine-through effect.

The analyses above further support that T2 time is a dominant contributor to ADC measure (24), and call for re-consideration on whether cellularity or high cell density contributes to tumor ADC. It has been perceived that malignant tissues' ADC is associated with malignant tissues' being generally more cellular than benign tissues and extra-cellular water molecule diffusion in these tissues is lower with anarchic cellular proliferation. While it is possible that a more malignant tumor will deviate more from the native tissue in composition, thus show more deviation in T2 time from native tissue, and thus so does ADC measure, some studies did not report a correlation between ADC measure and cellularity (59-63). For example, Sadeghi *et al.* (60) noted that '*This study*, *which takes into account the regional heterogeneity of gliomas*, *does not confirm the inverse correlation between ADC and cell density reported in previous studies. This finding underlines the impact of other determinants of water diffusivity within the complex microenvironment encountered in gliomas. As previously reported*, *edema*, *necrosis*, *and extracellular matrix components constitute some of such parameters that may influence ADC values within gliomas*.' The study of Rosenkrantz *et al.* (61) on pancreatic cancer showed no associations between ADCs of pancreatic adenocarcinoma and tumour grade or other adverse pathological features. Nonomura *et al.* (62) reported that there was no ADC difference between normal hematopoietic cell bone marrow without fat infiltration and lymphoma-related hypercellular bone marrow, despite lymphoma tissue had more compacted cells. *Table 3* shows

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Table 3 A list of ADC values of some musculoskeletal disorders and tumors of the body and brain

Authors	Materials/tissues	Mean ADC ($\times 10^{-3}$ mm^2/s)	Magnet[#]	b value (s/mm^2)[§§§]
Subhawong *et al.* (48)	Abscess in musculoskeletal soft tissue[§]	0.63	3.0 T	50, 400, 800
Erdogan *et al*. (49)	Abscess in brain	0.69	1.5 T	0, 1,000
Morán *et al.* (50)	Myxoma	2.38	1.5 T	0,300, 600, 1,000
Einarsdóttir *et al.* (51)	Myxoma	2.80	1.5 T	0, 600
Subhawong *et al.* (52)	Myxoid liposarcoma[§]	2.31	Unknown	Unknown
Hayashida *et al.* (53)	Chondrosarcoma	2.29	1.5 T	0, 500, 1,000
Ahlawat *et al*. (54)	Enchondroma[§§]	1.80	3.0 T	50, 400, 800
Subhawong *et al.* (48)	Ewings sarcoma[§]	0.80	3.0 T	50, 400, 800
Ahlawat *et al*. (54)	Osteosarcoma[##]	0.80	3.0 T	50, 400, 800
Feuerlein *et al*. (55)	Soft-tissue tumors (mixed)[##]	0.85	1.5 T	0, 150, 500, 1,000
Padhani *et al.* (9)	Multiple myeloma	0.88	1.5 T	50, 800 (or 900)
Padhani *et al.* (9)	Breast cancer bone marrow Met	0.94	1.5 T	50, 800 (or 900)
Byun *et al.* (17)	Sacrum Met (mixed)	0.78	1.5 T	0, 650
Balliu *et al.* (56)	Vertebral malignancies (mixed)	0.92	1.5 T	0, 500
Feuerlein *et al*. (55)	Liver malignancies (mixed)[##]	0.81	1.5 T	0, 150, 500, 1,000
Feuerlein *et al*. (55)	Colon/rectum malignancies (mixed)[##]	0.92	1.5 T	0, 150, 500, 1,000
Feuerlein *et al*. (55)	Uterus/ovaries malignancies (mixed)[##]	0.77	1.5 T	0, 150, 500, 1,000
Feuerlein *et al*. (55)	Skeletal Met (mixed)[##]	0.81	1.5 T	0, 150, 500, 1,000
Hepp *et al*. (41)	Prostate cancer	0.76	3.0 T	50, 500, 1,000, 2,000
Surov *et al*. (57)	Breast cancer liver Met	0.86	1.5 T	0, 600
Thormann *et al.* (58)	Hepatocellular carcinoma	0.93	1.5 T	0, 500
Oh *et al*. (43)	Gliomas	1.28	1.5 T	0, 1,000
Oh *et al*. (43)	Meningiomas/Met	1.10	1.5 T	0, 1,000
Stadnik *et al.* (59)	Gliomas	1.14	1.5 T	0, 300, 1,200

Data from tumors of the body and brain represent a few random selections for illustration only. [#], it is generally considered that diffusion is *per se* not a nuclear magnetic resonance phenomenon. Magnetic field strength should have little impact on ADC values measured (18,19); [§], result of a single case only; [§§], mineralization leading to lower ADC measures; [##], with limited case number; [§§§], ADC measure is affected by b value selection during data acquisition and the noise levels, however, besides muscle, perfusion contribution to ADC is small for most of the skeletal tissues. ADC, apparent diffusion coefficient; Met, metastasis.

ADCs of myeloma or metastatic malignancies in the bone do not demonstrate major ADC difference with other cancerous tissues such as liver malignancies, colon/rectum malignancies, uterus/ovaries malignancies, and prostate cancer. Brain tumors tend to have a relatively higher T2 time and a relatively higher ADC measure. For most of the tumors originated in the liver or pancreas, with increased T2 time which shifts toward 70 ms, these tumors have a reduced ADC relative to native tissues. For prostate cancer with a decreased T2 time which shifts toward 70 ms, prostate cancer also has a reduced ADC relative to the native tissue. With T2 time shifting away from 70 ms, brain tumors mostly are associated with increased ADC (24). For soft tissue tumours, Einarsdóttir *et al.* (51) reported ADC values of benign soft tissue tumours and sarcomas overlapped and could not be used to differentiate between the bulk of benign and malignant tumours. Maeda *et al.* (64) also reported that ADCs of benign and malignant soft-tissue

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tumors were not significantly different. Balliu *et al.* (56) reported that ADC does not help differentiate spine malignancy from spine infection. Razek *et al.* (65) reported that soft-tissue malignant tumors tend to have a lower mean ADC value than soft-tissue benign tumors. However, there was huge variation among individual cases depending on the histopathological types. An injection of gadolinium contrast agent, which will shorten T2 time of the tissues, has also been reported to be associated with a lower ADC measure (66,67) without the gadolinium contrast agent actually changing the diffusivity of the tissues. For the cases of prostate cancer and breast cancer, gadolinium agent will slightly shift the T2 times of these tissues toward 70 ms. It is also likely that the *in vivo* measurement of ADC is contaminated by bulk motion due to physiological motion (such as respiration and cardiovascular pulsing) and the vibration of MR scanner gradients during diffusion data acquisition. The contribution of cellularity to ADC may be of only minor importance in practice.

Another phenomenon of note is the so-called susceptibility T2* 'black-out', which is seen with structures having a very short intrinsic T2 signal due to very short T2* associated with iron or calcium content (68,69). It is known that hematomas can have a low ADC value. Susceptibility artifacts such as hemorrhage containing deoxyhemoglobin or hemosiderin result in unreliable ADC value calculations with pseudo-low ADC values (68,70,71). Assessing osteosarcoma or osteoblastic bone metastases can also be challenging sometimes due to the presence of this phenomenon (72).

The analyses in this article re-emphasize the notion that, for interpretation of ADC value of any tissue, this tissue's T2 time should be always referred (24). Moreover, some authors reported that ADC does not offer superiority over T2 time in a number of diagnostic analyses. For intracerebral tumors, Oh *et al.* (43) reported T2 values were more useful than ADC for characterizing contrast enhancing tumor and immediate-edema regions of glioma, meningiomas and metastases. Stadnik *et al.* (59) reported that the diffusion-weighted images and ADC maps of gliomas were less useful than the T2-weighted and contrast-enhanced T1-weighted images in definition of tumor boundaries. The ADC values of solid gliomas, metastases, and meningioma were in the same range. In a study of glioma patients, Kinoshita *et al.* (73) reported that ADC was unable to show a significant correlation with ^{11}C-methionine uptake (as shown on positron emission tomography) or with tumor cell density; however, a combination of T1 and T2 relaxation time correlated both with methionine uptake and tumor cell density. Cieszanowski *et al.* (74) reported significantly higher sensitivity and accuracy of T2 time than ADC for diagnosing hepatic malignancy. ADC maps may suffer from alignment errors between images of different b values and also low signal-to-noise ratio from diffusion-weighted imaging. Within the framework of diffusion weighted imaging, a number of pitfalls have also been noted with intravoxel incoherent (IVIM) analysis (21,75-77). The additional benefits of ADC over T2 time or signal intensity on properly T2 weighted images should be carefully studied further for musculoskeletal application.

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Footnote

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1392/coif). YXJW serves as the Editor-in-Chief of *Quantitative Imaging in Medicine and Surgery*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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