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Equine flexor tendon imaging part 2 – current status and future directions in advanced diagnostic imaging, with focus on the deep digital flexor tendon

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Review

Equine flexor tendon imaging part 2 – current status and future directions in advanced diagnostic imaging, with focus on the deep digital flexor tendon

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Abstract

Flexor tendon injuries are a common cause of lameness and early retirement in equine athletes. Whilst ultrasonography is most frequently utilized, advanced diagnostic imaging modalities are becoming more widely available for detection and monitoring of flexor tendon lesions. Part two of this literature review aims to detail the current experience with low- and high-field magnetic resonance imaging (MRI) and computed tomography (CT) for the diagnosis of equine flexor tendinopathy. Implications of the~~Recently described approaches including~~ 'magic angle' artefact~~MRI~~ as well as injection techniques and the use of contrast are discussed. Besides lesion detection, future developments in tendon imaging focus on gaining enhanced structural ~~and functional~~ information about the tendon architecture with the prospect to prevent injury. Techniques as described ~~in~~ for the assessment of the human Achilles tendon including ultra-high field MRI and positron emission tomography are highlighted.

Keywords: Computed tomography; Horse; Magnetic resonance imaging; Tendinopathy~~on~~

Introduction

Superficial digital~~Equine~~ flexor tendon (SDFT) injury is most commonly seen in racing Thoroughbreds whereas injuries of the deep digital flexor tendon (DDFT) affect horses performing in a wide variety of disciplines (Takahashi et al., 2004; Lam et al., 2007; Smith et al., 2007; Arensburg et al., 2011). The majority of DDFT lesions involve the distal aspect of the tendon and are associated with concurrent pathology of the podotrochlear~~navicular~~ apparatus ~~and palmar foot pain~~ in approximately 51-79% of cases (Blunden et al., 2006; Blunden et al., 2009; Vanel et al., 2012; Cillan-Garcia et al., 2013). Clinical examination and ultrasonography are often sufficient for the diagnosis of SDFT injury. The increasing availability of advanced diagnostic imaging modalities for the assessment of the equine digit has however greatly improved the diagnosis of DDFT pathology over the past two decades, particularly as the hoof capsule limits the utility of ultrasonography in this area (Tucker and Sande, 2001; Mair and Kinns, 2005; Dyson and Murray, 2007; Sherlock et al., 2015; Jones et al., 2019). For the second part of this review the current literature was systematically assessed as described in review part 1 in order to provide an overview of recent developments and future prospects for equine flexor tendon advanced diagnostic imaging. The following search terms were used in PubMed, Medline and Google Scholar without restrictions: 'tendon' AND 'magnetic resonance imaging' OR 'computed tomography' AND 'equine' OR 'horse'. Additional studies were identified by searching the reference list of eligible articles.

~~Low-field~~ Magnetic resonance imaging~~RI~~

MRI for the evaluation of soft tissue injuries in equine patients was first introduced in the early 1990s and has since become widely used~~the gold standard~~ for tendon and ligament imaging especially in the equine digit (Park et al., 1987; O'Callaghan, 1991; Denoix, 1994;

Kotani et al., 2000; King et al., 2013; Bubeck and Aarsvold, 2018). An increasing number of low-field (0.25 to- <1 1 Tesla) open MRI units are installed in equine referral practices across Europe, the US and other countries, and several studies have proven a good correlation between low- and high-field MR imaging findings and histopathological diagnosis of tendon disease (Kasashima et al., 2002; Murray et al., 2004; Blunden et al., 2006; Murray et al., 2006; Blunden et al., 2009; Murray et al., 2009; Karlin et al., 2011; Sherlock et al., 2015) (Table 1). Additionally, tendon injuries caused by foot penetrations or distal limb wounds can be diagnosed with high accuracy using standing low-field MRI (del Junco et al., 2012; Meehan, 2017; Schiavo et al., 2018; Sherlock et al., 2019).

Low-field MRI

MR image acquisition: the 'magic angle'

The 'magic angle' effect can impact on the interpretation of MR images depending on the positioning of the limb in the magnetic field. The artefact is the result ofcharacterized by increased T2 relaxation timesignal that occurs when collagen fibres (which through strong dipolar interaction typically have very low MR signal) are oriented at approximately 55° to the main magnetic field (B_0) during image acquisition (Erickson et al., 1991; Erickson et al., 1993; Bydder et al., 2007; Murray et al., 2009). The 'magic angle' effect typically manifests as focally increased signal and is usually found on short echo time sequences including T1-weighted fast spin echo and proton density-weighted sequences but may also be observed on other sequences (Peh and Chan, 1998; Li and Mirowitz, 2003; Richardson et al., 2018). The common sites and appearance of the artefact are well documented for the DDFT and ligaments including the collateral ligaments of the distal interphalangeal joint (Spriet et al., 2007; Smith et al., 2008; Spriet and McKnight, 2009; Spriet and Zwingenberger, 2009; Gutierrez-Nibeyro et al., 2011). A recent report emphasized the importance of the position of

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the long axis of the limb perpendicular to the magnetic field also for low-field MRI of the SDFT. Leaning to one side as well as internal or external limb rotation during MR image acquisition in the standing horse may create a 'magic angle' artefact in the SDFT at the level of the pastern that should not be confused with tendon pathology (Fig. 1) (Sherlock and Mair, 2016).

MRI for monitoring of tendon lesions

Since MRI has been established as a sensitive tool for the diagnosis of tendinopathies in the equine patient, the value of repeated MRI for monitoring purposes has been further investigated. Sequential MRI evaluation of DDFT lesions in clinical cases has shown that resolution of STIR-FSE and T2-FSE signal changes over time appear to be positive prognostic indicators, whilst most lesions remain visible on T1-GRE and PD images even in cases with excellent outcome (Holowinski et al., 2010; Vanel et al., 2012). Horses with T1-GRE hyperintense DDFT lesions over 30mm in length or over 10% cross-sectional area, as well as horses with persistent STIR-FSE signal or with concurrent lesions in the foot, are less likely to return to their previous level of exercise (~~Dyson et al., 2005; Dyson and Murray, 2007;~~ Vanel et al., 2012).

The evolution~~development~~ of different DDFT lesion types varies when assessed over time. Dorsal border lesions showed a more rapid reduction in T2*-GRE volume and ratiometric intensity (ratio between lesion and adjacent cortical bone) than parasagittal and core lesions in clinical cases that were followed over a 6-month period (Milner et al., 2012). No correlation between lameness and lesion signal intensity was found in this study, but long-term telephone follow-up (18 months) of a larger group of horses confirmed that dorsal border lesions seem to have a favourable prognosis for return to some level of activity~~ridden~~

~~exercise~~ (73%) when compared to other lesion types (core lesions 41%; parasagittal splits 50%) (Cillan-Garcia et al., 2013). However, overall only approximately 25% of these horses returned to their previous level of exercise. The~~is~~ study additionally showed an effect of lesion location with a worse prognosis identified for insertional or suprasesamoidean lesions of the DDFT when compared to lesions at the level of the navicular bone. L~~that l~~esions affecting both lobes of the DDFT were~~are~~ not necessarily associated with a worse prognosis than uniaxial defects (Cillan-Garcia et al., 2013).

Ultrasonography currently remains the most practical imaging modality for the diagnosis and monitoring of SDFT lesions in a clinical setting (Bubeck and Aarsvold, 2018). It is however important to note that the area of maximal cross-sectional injury in experimentally induced SDFT lesions older than 4 weeks appears approximately 18% smaller on ultrasonographic images when compared to standing low-field MRI (Schramme et al., 2010; Karlin et al., 2011). Similar results were found in naturally occurring SDFT lesions~~other studies~~ and should be taken into consideration when adjusting the exercise program of a horse with SDFT tendinopathy based on ultrasonographic assessment alone (~~Schramme et al., 2010;~~ Berner et al., 2016). During sequential MRI examination, SDFT lesions follow a pattern of signal change that differs from the pattern observed in DDFT lesions over time. MR signal decreases earlier in T2-weighted images than in STIR-FSE images in the SDFT (Schramme et al., 2010; Karlin et al., 2011; Berner et al., 2016; Berner, 2017; Berner et al., 2020).

High-field MRI

Most high-field MRI systems with a field strength of 1 Tesla (T) and above are installed in larger referral centres. Examination is usually performed in a closed-bore magnet

and requires the horse to be anaesthetised (Lutter et al., 2015). Due to the higher signal-to-noise ratio and corresponding increased image contrast and resolution, the tendon margins are better defined, and subtle lesions appear more conspicuous on high-field MR images when compared to standing low-field MRI (Ghazinoor et al., 2007; Murray et al., 2009). Whilst tendon lesions and adhesions are generally detected on low- and high-field MR images, small focal lesions (≤ 1 mm in diameter) and subtle dorsal fibrillation of the DDFT may be visible on high-field MRI only (Murray et al., 2009).

'Magic angle MRI'

Similar to the appearance on low-field MRI where the B_0 magnetic field is oriented vertically, the 'magic angle' effect at the distal aspect of the DDFT can be recognised mainly on T1-weighted high-field MR images, when the long axis of the tendon is oriented at approximately 55° (+/- 5-7°) to the horizontally oriented static magnetic field (Busoni and Snaps, 2002; Spriet and McKnight, 2009; Werpy et al., 2010). The artefact is characterised by a hyperintense signal and can impact on the interpretation of MR images (Erickson et al., 1991; Erickson et al., 1993). Since tendons generally present with little to no signal on MR images, the intentional application of the 'magic angle' effect has been proposed to further investigate the available signal of the tendon structure. The so called 'magic angle MRI' allows sufficient signal to be obtained using the standard pulse sequences of clinical MRI systems (Bydder et al., 2007). Using this technique, an increased T1 relaxation time has been reported in cases of chronic Achilles tendinopathy in humans (Marshall et al., 2002; Oatridge et al., 2003).

In an initial 'magic angle MRI' study on equine specimens, reference values for the normal T1 relaxation times of the equine SDFT, DDFT and suspensory ligament were

determined (Spriet et al., 2011). To further assess possible changes in T1 relaxation associated with tendinopathy, both laser-induced and~~as well as~~ naturally occurring SDFT lesions were subsequently evaluated (Spriet et al., 2012). All naturally occurring lesions were visible on conventional as well as on 'magic angle' MR images. Based on the histological findings the authors state however, that 'magic angle MRI' might be advantageous for the identification of diffuse changes in tendon composition, that appeared hypointense on conventional MR imaging (Spriet et al., 2012). Whilst the feasibility of 'magic angle MRI' has been demonstrated in high-and low-field MRI systems, the adequate positioning of the limb may still prove to be a challenge in an *in vivo* setting (Spriet et al., 2012; Horstmeier et al., 2019).

Influence of local injection on MRI interpretation

Research assessing the influence of diagnostic analgesia on MR image interpretation showed that perineural analgesia of the palmar digital nerves, as well as intra-synovial analgesia of the navicular bursa and the distal interphalangeal joint, do not significantly alter MR images of the distal limb at 1.5 T (Black et al., 2013). Only the injection of 15 ml mepivacaine into the digital flexor tendon sheath caused an iatrogenic increase in synovial fluid volume as detected on MRI at 24 and 72 hours post injection (Black et al., 2013). The study additionally described that needle tracts could not be appreciated consistently at any injection site apart from the site of the navicular bursa injection, where some evidence for a needle tract was detected in 10/15 limbs at 72 hours post injection.

Another study further investigated the influence of saline injection (30-35 ml) into the digital flexor tendon sheath for the purpose of enhanced ultrasonographic and 1.5 T high-field MR image interpretation (Daniel et al., 2019). The study showed that the presence of

fluid significantly improved the delineation of the DDFT in both imaging modalities and the visualisation of the margins of the SDFT on MR images. As the technique did not introduce any artefacts or altered the dimensions of the intra-thecal structures, further evaluation in clinical cases should be of value particularly for the detection of marginal tendon lesions. It is however important to consider that patients might be reluctant to stand during low-field MRI following distention of the digital flexor tendon sheath. Consequently, the technique appears to be more suited for high-field MR evaluation.

In order to facilitate assessment of the dorsal border of the DDFT at the level of the navicular bone, the injection of the navicular bursa with saline (6-10 ml) or a mixture of saline and contrast medium (5-6 ml, 1:1 ratio of 0.9% saline: Diatrizoate Meglumine and Diatrizoate Sodium; Hypaque-76®) has been proposed (Schramme et al., 2009; Maher et al., 2011). The distension of the navicular bursa physically separates the palmar surface of the navicular bone from the dorsal margin of the DDFT and allows adhesions, DDFT fibrillation and tendon splits at this level to be recognized more readily. The limitations of the technique include the time required for the navicular bursa injection under radiographic guidance, and the risk of rupture of the navicular bursa, especially if a volume in excess of 5 ml is injected (Schramme et al., 2009; Maher et al., 2011). Alternatively, the distension of the distal interphalangeal joint with saline (20-35 ml) alters the position of the proximal recess of the navicular bursa and enhances the visualisation of the dorsal border of the DDFT, similar to the direct approach to the navicular bursa (McGill et al., 2015). Both techniques are described to be more reliable in the non-weightbearing limb when no pressure is exerted between the navicular bone and the DDFT and are therefore probably more suitable for high-field MRI *in vivo* (Maher et al., 2011; McGill et al., 2015).

Contrast-enhanced MRI

Gadolinium-based contrast-enhanced MRI is routinely performed for~~in~~ human and small animal neurologic, oncologic and vascular imaging (Owen, 2018; Scott, 2018). Gadolinium shortens the relaxation time constants (T1 and T2) of the tissues, which leads to an increase in signal intensity, especially in T1-weighted images (Lin and Brown, 2007). First clinical reports recommended an intra-venous gadopentate dimeglumine dose of 0.1 ml/kg (50 ml/horse) for musculoskeletal contrast-enhanced MRI in horses (Judy et al., 2008; Saveraid and Judy, 2012; Daniel et al., 2013). The authors described the potential for an improved recognition and assessment of tendon lesions, similar to the human Achilles tendon, where a correlation between contrast enhancement and the severity of tendon lesions has been demonstrated in a number of clinical cases (Shalabi et al., 2002; Richards et al., 2010).

In order to decrease the volume and associated expense of gadolinium required for contrast-enhanced MRI in horses, regional limb perfusion with gadopentate dimeglumine (5 ml in 5 ml 0.9% saline) via the palmar/plantar digital vein at the level of the mid metacarpus/metatarsus was evaluated in a prospective clinical study (Aarsvold et al., 2018). Pre- and post-contrast high-field (1.5 T) MRI was performed in anaesthetized horses in lateral recumbency. C~~The c~~ontrast enhancement in the distal limb was adequate provided the tourniquet was secured in place. Multiple lesions were identified and were mostly visible on pre-contrast as well as contrast-enhanced MR images. The authors describe, however, that the technique aids the characterisation of lesions including adhesions and neovascularisation of the DDFT (Aarsvold et al., 2018). In the standing horse the approach may be limited due to difficulties in ensuring patients stand still for the requisite amount of time for the examination

post tourniquet application. Additionally, it might be challenging to replicate the exact position of the foot in the magnet pre- and post contrast injection.

A further study compared systemic intra-venous injection with regional intra-arterial injection of gadolinium in a group of horses with lameness localized to the foot (De Zani et al., 2018). The injection of 0.02 ml/kg of gadolinium in the radial artery resulted in a higher ratio of MRI contrast enhancement when compared to the systemic intra-venous route (0.1 ml/kg). Whilst the tendon tissue appeared generally not highly vascularised, significant enhancement of the DDFT and peritendinous tissue was noted in the area of suspected pathological lesions (De Zani et al., 2018).

The contrast enhancement in association with tendinopathy is most likely related to an increased capillary permeability and diffusion of blood into the interstitial space in the acute stages of the injury. Additionally, neovascularisation and granulation tissue formation are suspected to show increased contrast uptake. However, histological studies of contrast-enhancing lesion in the equine distal limb are currently lacking (Shalabi et al., 2002; Saveraid and Judy, 2012; Nelson et al., 2017).

Side effects of the administration of gadolinium-based contrast agents are described in human and small animal patients, but no severe adverse reactions were encountered in the aforementioned equine studies (Wible et al., 2001; Grobner and Prischl, 2007; Lin and Brown, 2007; Girard and Leece, 2010; Saveraid and Judy, 2012; Prince et al., 2017; Aarsvold et al., 2018; De Zani et al., 2018). A recent review of the use of contrast media in horses classified the risk associated with the administration of gadolinium generally as low, provided horses do not suffer underlying renal disease or dehydration (Nelson et al., 2017).

Future research should further ascertain the benefits of contrast-enhanced over standard MRI for the assessment of tendon lesions and identify how imaging findings correlate with histopathology. Additionally, the combined approach of contrast-enhanced and 'magic angle MRI' as described for the human Achilles tendon might be of interest for equine flexor tendon imaging (Marshall et al., 2002).

Ultra-high field MRI

The high-field MRI systems currently installed in veterinary centres for clinical applications operate at a field strength of 1.5 to 3 T. Magnets used in humans for clinical purposes have now reached 7 T, and preclinical research ultra-high field MRI systems exceeding a field strength of 10 T are available (Alizai et al., 2018; Ladd et al., 2018).

Low- and high-field MRI facilitates the detection and assessment of tendon lesions, but the visualisation of the tendon structure remains difficult. The very short transverse relaxation time of normal tendon tissue, with the relatively long echo times used in conventional clinical MRI sequences usually result in the complete decay of tendon signal before it can be sampled (Juras et al., 2012; Guidetti et al., 2018; Juras et al., 2019). With increasing field strength and signal-to-noise ratio, and the use of ultrashort echo time (UTE) and other sequences, MR images of the finer tendon structural components can be obtained (Fig. 2) (Robson et al., 2004; Du et al., 2010; Moser et al., 2012; Juras et al., 2013; Chang et al., 2015; Foure, 2016). In man, ultra-high field MRI is utilized to visualise the fascicular pattern of the Achilles tendon *in vivo* (Han et al., 2014; Foure, 2016; Juras et al., 2019).

Ultra-high field MRI of the equine SDFT

Ultra-high field MRI (9.4 T) of the equine SDFT facilitates the detailed assessment of the tendon structure with clear delineation of the tendon fascicles and interfascicular matrix (Fig. 2 A + B). Additionally, T2*-weighted 3D-FISP gradient echo transverse images provide a comprehensive picture for the characterisation of tendon lesions (Fig. 2C). At this stage the size of the radiofrequency coil and the time required to obtain this high level of anatomical detail preclude the *in vivo* assessment of tendon lesions in horses. The cost and technical expertise involved with MR imaging at higher field strength limits its availability in veterinary medicine, however, ultra-high field MRI offers promising prospects for musculoskeletal imaging as clinical progress continues (Alizai et al., 2018; Ladd et al., 2018).

Computed tomography

The limited availability of MRI has led to the investigation of alternative modalities for soft tissue advanced diagnostic imaging in equine orthopaedics (Tucker and Sande, 2001; Puchalski, 2012; Jones et al., 2019). A study comparing MRI and CT for the assessment of the equine distal limb found similar scores for the visibility of the DDFT in the area of the pastern for both modalities, but the distal DDFT at the level of insertion showed better visualisation scores with low-field MRI (Vallance et al., 2012a). Likewise, the classification of DDFT lesions varies depending on the imaging modality used for interpretation. More lesions of the distal DDFT were detected with low-field MRI but lesions at the level of the pastern as well as abrasions and mineralisation of the DDFT were more likely to be diagnosed with CT in a cohort of clinical cases (Fig. 3) (Vallance et al., 2012b). Additional reports comparing both, MRI and CT imaging findings of the same subject with results of histopathological examination would give further insight and support image interpretation (Whitton et al., 1998; Puchalski et al., 2009).

Contrast-enhanced computed tomography

The contrast media used for CT studies in equine patients are usually iodinated solutions that strongly attenuate X-rays and highlight areas of increased vascular perfusion or permeability (Bushberg et al., 2012; Nelson et al., 2017). Following acquisition of pre-contrast images t~~T~~he intra-vascular or intra-thecal route of administration may be chosen for contrast-enhanced CT imaging of the equine distal limb (Puchalski, 2012; Nelson et al., 2017).

There are some reports of intra-venous contrast studies in the horse (Hunter et al., 2016; Walker et al., 2017). However, the technique most commonly described is the regional intra-arterial injection of contrast medium, including placement of a catheter in the medial palmar artery at the level of the carpometacarpal joint under ultrasonographic guidance in the anaesthetised horse. Steady-state infusion of a 1:1 dilution of ionic-iodinated contrast in saline is subsequently maintained with a remotely controlled pressure injector (2 ml/s), starting 3-5 seconds prior to CT examination (Collins et al., 2004; Puchalski et al., 2005; Puchalski et al., 2007; Puchalski et al., 2009; Pollard and Puchalski, 2011b). Whilst tendon lesions are less common in the hindlimb, contrast application via catheterisation of the lateral dorsal metatarsal artery is also described (van Hamel et al., 2014) (Fig. 4). The normal CT anatomy and attenuation values for tendon and ligament before and after intra-arterial contrast administration have been documented in detail (Tietje et al., 2001; Puchalski et al., 2007; Vallance et al., 2012a; Claerhoudt et al., 2014). The DDFT generally shows a slight but significant increase in post-contrast attenuation (8-17 HU) that potentially impairs on the clear anatomical visualisation of the tendon (Puchalski et al., 2007; Vallance et al., 2012a).

DDFT lesions in the area of the foot are usually characterised by marked contrast enhancement (> 20 HU) that may be central, peripheral or diffuse (Puchalski et al., 2009; Puchalski, 2011; Vallance et al., 2012b; van Hamel et al., 2014). Lack of contrast enhancement has been occasionally observed in dorsal border lesions of the DDFT. A sensitivity of 93% for lesion detection was determined following histopathological examination of the affected tissue in one study (van Hamel et al., 2014). All false negative results obtained in this study were at the level of the navicular bone where the visibility of the DDFT is most limited on CT images (Vallance et al., 2012a; van Hamel et al., 2014). Clinical studies have shown that lesions of the DDFT can also be diagnosed based on non-contrast-enhanced CT (Tietje et al., 2001; Jones et al., 2019). However, lesions in the area of the DDFT insertion were more likely to be identified post-contrast in one study (Vallance et al., 2012b).

CT contrast tenography may aid the evaluation of the flexor tendons as they course through the digital flexor tendon sheath (Fig. 5~~4~~). Consistent delineation of the flexor tendon borders and the *manica flexoria* has been described after intra-thecal injection of nonionic-iodinated contrast solution (60 ml) into the digital flexor tendon sheath of cadaver limbs without flexor tendon pathology (Lacitignola et al., 2015; Agass et al., 2018). Further research should confirm the value of this technique for diagnostic purposes and pre-surgical planning.

Adverse reactions to the intravascular administration of iodinated contrast are rare in horses but may include a transient increase in heart rate and blood pressure as well as local or generalised skin reactions (Gunkel et al., 2004; Pollard and Puchalski, 2011a; Nelson et al., 2017). CT technology is advancing rapidly and the resolution of images obtained for the

assessment of clinical cases has considerably increased over the past decade (Puchalski, 2012; Riggs, 2018). High slice number multidetector CT scanners are becoming more widely available and first examples of distal limb examination in standing horses have been reported (Desbrosse et al., 2008; Koch et al., 2020; Mageed 2020; Pauwels et al., 2021). In contrast to MR imaging ~~W~~CT does not offer the capability of accurately detecting the fluid content within a tendon lesion to date. However, with its improved image quality and fast acquisition time, CT may provide a practical alternative to MRI for advanced diagnostic imaging of the equine flexor tendons (Riggs, 2018; Jones et al., 2019). Future research should show whether CT imaging is comparable to MRI regarding the assessment of lesion progression over time. Additionally, patient tolerance regarding contrast procedures in the standing horse warrants further investigation.

Positron emission tomography

Positron Emission tomography (PET) is a nuclear medicine imaging technique mainly used in the field of human oncology, but orthopaedic applications are also described in man (Fischer et al., 2010; Fischer, 2013; Kim et al., 2015; Eliasson et al., 2016; Aide et al., 2019). In contrast to gamma scintigraphy where planar images are obtained after the injection of a radioactive agent, PET acquires cross-sectional images allowing for three-dimensional assessment of the region of interest (Spriet, 2019). PET is usually combined with CT in order to obtain functional and structural information. As this setup is currently difficult to realise in large patients like horses, a PET scanner used for preclinical brain research has been adapted for PET imaging of the equine distal limb. First reports of PET imaging in equine orthopaedics mainly describe the benefits of the technique for the detection of osseous lesions and enthesopathy (Spriet et al., 2016; Spriet et al., 2018; Spriet et al., 2019; Norvall et al., 2020). PET imaging has been applied for the monitoring of the healing response after

Achilles tendon rupture in human patients and increased uptake of the glucose tracer ^{18}F-fluorodeoxyglucose was detected in horses with SDFT and DDFT tendinopathy in one exploratory study (Eliasson et al., 2016; Spriet et al., 2016). Future studies will further determine the value of PET imaging for the assessment of the equine flexor tendons in clinical cases (Spriet, 2019).

Conclusion

The rapid and ongoing technological progress and particularly the influence of modern computing has led to the development of a multitude of approaches for soft tissue imaging. Not all techniques described in preclinical studies or human orthopaedic research will be economical or practical enough to be carried through into veterinary clinical diagnostics. However, the last two decades have shown how fast advanced diagnostic imaging modalities including MRI and CT have been integrated in equine orthopaedics at referral level. Both modalities have benefits and disadvantages, particularly for the assessment of flexor tendon injuries. Detailed knowledge of MRI and CT approaches including the implications of the 'magic angle' and the use of injection techniques and contrast should aid image interpretation and selection of the appropriate modality. As diagnostic imaging is crucial for the diagnosis and monitoring of equine tendinopathy and potentially aids ~~has high potential for~~ the prevention of tendon injury, there is ongoing demand for future studies in this developing field of research.

Conflict of intertest statement

None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of the paper.

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Table 1

Overview of the literature validating magnetic resonance imaging (MRI) in the equine distal limb for the assessment of the superficial digital flexor tendon (SDFT) and the deep digital flexor tendon (DDFT).

Low-field MRI	Literature source	Area examined	No of horses
0.2 T	Kasashima et al., 2002	SDFT	6
0.27 T	Murray et al. 2009	SDFT / DDFT	10
0.25 T	Karlin et al., 2011	SDFT	8
0.27 T	Sherlock et al., 2015	DDFT	26
High-field MRI			
1.5 T	Murray et al., 2004	DDFT (distal)	38
1.5 T	Murray et al., 2006a	DDFT (distal)	32
1.5 T	Murray et al., 2006b	DDFT (distal)	34
1.5 T	Murray et al., 2009	SDFT / DDFT	10
1.5 T	Blunden et al., 2006	DDFT (distal)	32
1.5 T	Blunden et al., 2009	DDFT (distal)	46

Figure legends

Fig 1. T1-weighted gradient echo (GRE) FAST transverse low-field (0.27T) magnetic resonance image of the equine distal limb at proximal pastern level (lateral is to the left~~right~~). (A) Note the increased T2 signal intense 'magic angle' artefact at the mid- to lateral aspect of the superficial digital flexor tendon (SDFT) (black arrow) as observed with 'leaning in' or lateral rotation of the limb during image acquisition. (B) lesion of the medial lobe of the SDFT (white arrow) (Image courtesy of Birte Drees, Lucidity Diagnostics 2020).

Fig. 2. T2*-weighted 3D-FISP (fast imaging with steady-state free precession) gradient echo transverse MR images of the superficial digital flexor tendon (lateral is to the left). (A) 3-year old Irish Sports Horse mare without pre-existing orthopaedic condition. (B) 25-year old Thoroughbred mare without a history of orthopaedic disease. Thinning of the interfascicular matrix is evident as a result of ageing. (C) 8-year old Thoroughbred gelding with clinical SDFT tendinopathy.

Fig. 3. Transverse computed tomographic (CT) images (soft tissue window without contrast) of the deep digital flexor tendon (DDFT) at the level of the lower pastern (lateral is to the left). (A) Longitudinal split of the lateral lobe of the DDFT (white arrow) with moderate distension of the navicular bursa (black arrow). (B) Dorsal border lesion of the DDFT (white arrow) (Images courtesy of Carolin Müller, Lucidity Diagnostics 2020).

Fig. 4. Contrast enhanced computed tomographic images (bone window) showing the deep digital flexor tendon (DDFT) of the left hindlimb of a 10-year-old Warmblood showjumper, acquired during steady-state infusion of ionic-iodinated contrast in saline (1:1; 2ml/s) via the lateral dorsal metatarsal artery (lateral is to the left). (A) Note the increased contrast

enhancement associated with a core lesion of the DDFT in zone 4B (white arrow). (B) Additionally, perilesional contrast attenuation was evident in both lobes of the DDFT in zone P2A (white arrows) in the same horse.

Fig. 54. Computed tomographic (CT) images of the flexor tendons at the level of the digital flexor tendon sheath with (B + D) and without (A + C) intra-thecal application of nonionic-iodinated contrast. The superficial and deep digital flexor tendons can be recognized on transverse (A) and sagittal (C) CT images using the soft tissue window. The outline of the *manica flexoria* (white arrow) and the flexor tendons is highlighted following injection of the digital flexor tendon sheath with contrast (B + D) (lateral is to the left on Fig. 5 A and B) (Images courtesy of Carolin Müller, Lucidity Diagnostics 2020).

Review

Equine flexor tendon imaging part 2 – current status and future directions in advanced diagnostic imaging, with focus on the deep digital flexor tendon

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Abstract

Flexor tendon injuries are a common cause of lameness and early retirement in equine athletes. Whilst ultrasonography is most frequently utilized, advanced diagnostic imaging modalities are becoming more widely available for detection and monitoring of flexor tendon lesions. Part two of this literature review aims to detail the current experience with low- and high-field magnetic resonance imaging (MRI) and computed tomography (CT) for the diagnosis of equine flexor tendinopathy. Implications of the 'magic angle' artefact as well as injection techniques and the use of contrast are discussed. Besides lesion detection, future developments in tendon imaging focus on gaining enhanced structural information about the tendon architecture with the prospect to prevent injury. Techniques as described for the assessment of the human Achilles tendon including ultra-high field MRI and positron emission tomography are highlighted.

Keywords: Computed tomography; Horse; Magnetic resonance imaging; Tendinopathy

Introduction

Superficial digital flexor tendon (SDFT) injury is most commonly seen in racing Thoroughbreds whereas injuries of the deep digital flexor tendon (DDFT) affect horses performing in a wide variety of disciplines (Takahashi et al., 2004; Lam et al., 2007; Smith et al., 2007; Arensburg et al., 2011). The majority of DDFT lesions involve the distal aspect of the tendon and are associated with concurrent pathology of the podotrochlear apparatus in approximately 51-79% of cases (Blunden et al., 2006; Blunden et al., 2009; Vanel et al., 2012; Cillan-Garcia et al., 2013). Clinical examination and ultrasonography are often sufficient for the diagnosis of SDFT injury. The increasing availability of advanced diagnostic imaging modalities for the assessment of the equine digit has however greatly improved the diagnosis of DDFT pathology over the past two decades, particularly as the hoof capsule limits the utility of ultrasonography in this area (Tucker and Sande, 2001; Mair and Kinns, 2005; Dyson and Murray, 2007; Sherlock et al., 2015; Jones et al., 2019). For the second part of this review the current literature was systematically assessed as described in review part 1 in order to provide an overview of recent developments and future prospects for equine flexor tendon advanced diagnostic imaging. The following search terms were used in PubMed, Medline and Google Scholar without restrictions: ‘tendon’ AND ‘magnetic resonance imaging’ OR ‘computed tomography’ AND ‘equine’ OR ‘horse’. Additional studies were identified by searching the reference list of eligible articles.

Magnetic resonance imaging

MRI for the evaluation of soft tissue injuries in equine patients was first introduced in the early 1990s and has since become widely used for tendon and ligament imaging especially in the equine digit (Park et al., 1987; O'Callaghan, 1991; Denoix, 1994; Kotani et al., 2000; King et al., 2013; Bubeck and Aarsvold, 2018). An increasing number of low-field

(0.25 to <1 Tesla) open MRI units are installed in equine referral practices across Europe, the US and other countries, and several studies have proven a good correlation between low- and high-field MR imaging findings and histopathological diagnosis of tendon disease (Table 1). Additionally, tendon injuries caused by foot penetrations or distal limb wounds can be diagnosed with high accuracy using standing low-field MRI (del Junco et al., 2012; Meehan, 2017; Schiavo et al., 2018; Sherlock et al., 2019).

Low-field MRI

MR image acquisition: the 'magic angle'

The 'magic angle' effect can impact on the interpretation of MR images depending on the positioning of the limb in the magnetic field. The artefact is the result of increased T2 relaxation time that occurs when collagen fibres (which through strong dipolar interaction typically have very low MR signal) are oriented at approximately 55° to the main magnetic field (B_0) during image acquisition (Erickson et al., 1991; Erickson et al., 1993; Bydder et al., 2007; Murray et al., 2009). The 'magic angle' effect typically manifests as focally increased signal and is usually found on short echo time sequences including T1-weighted fast spin echo and proton density-weighted sequences (Peh and Chan, 1998; Li and Mirowitz, 2003; Richardson et al., 2018). The common sites and appearance of the artefact are well documented for the DDFT (Spriet et al., 2007; Smith et al., 2008; Spriet and McKnight, 2009; Spriet and Zwingenberger, 2009; Gutierrez-Nibeyro et al., 2011). A recent report emphasized the importance of the position of the long axis of the limb perpendicular to the magnetic field also for low-field MRI of the SDFT. Leaning to one side as well as internal or external limb rotation during MR image acquisition in the standing horse may create a 'magic angle' artefact in the SDFT at the level of the pastern that should not be confused with tendon pathology (Fig. 1) (Sherlock and Mair, 2016).

MRI for monitoring of tendon lesions

Since MRI has been established as a sensitive tool for the diagnosis of tendinopathies in the equine patient, the value of repeated MRI for monitoring purposes has been further investigated. Sequential MRI evaluation of DDFT lesions in clinical cases has shown that resolution of STIR-FSE and T2-FSE signal changes over time appear to be positive prognostic indicators, whilst most lesions remain visible on T1-GRE and PD images even in cases with excellent outcome (Holowinski et al., 2010; Vanel et al., 2012). Horses with T1-GRE hyperintense DDFT lesions over 30mm in length or over 10% cross-sectional area, as well as horses with persistent STIR-FSE signal or with concurrent lesions in the foot, are less likely to return to their previous level of exercise (Vanel et al., 2012).

The evolution of different DDFT lesion types varies when assessed over time. Dorsal border lesions showed a more rapid reduction in T2*-GRE volume and ratiometric intensity (ratio between lesion and adjacent cortical bone) than parasagittal and core lesions in clinical cases that were followed over a 6-month period (Milner et al., 2012). No correlation between lameness and lesion signal intensity was found in this study, but long-term telephone follow-up (18 months) of a larger group of horses confirmed that dorsal border lesions seem to have a favourable prognosis for return to some level of activity (73%) when compared to other lesion types (core lesions 41%; parasagittal splits 50%) (Cillan-Garcia et al., 2013). However, overall only approximately 25% of these horses returned to their previous level of exercise. The study additionally showed an effect of lesion location with a worse prognosis identified for insertional or suprasesamoidean lesions of the DDFT when compared to lesions at the level of the navicular bone. Lesions affecting both lobes of the DDFT were not necessarily associated with a worse prognosis than uniaxial defects (Cillan-Garcia et al., 2013).

Ultrasonography currently remains the most practical imaging modality for the diagnosis and monitoring of SDFT lesions in a clinical setting (Bubeck and Aarsvold, 2018). It is however important to note that the area of maximal cross-sectional injury in experimentally induced SDFT lesions older than 4 weeks appears approximately 18% smaller on ultrasonographic images when compared to standing low-field MRI (Schramme et al., 2010; Karlin et al., 2011). Similar results were found in naturally occurring SDFT lesions and should be taken into consideration when adjusting the exercise program of a horse with SDFT tendinopathy based on ultrasonographic assessment alone (Berner et al., 2016). During sequential MRI examination, SDFT lesions follow a pattern of signal change that differs from the pattern observed in DDFT lesions over time. MR signal decreases earlier in T2-weighted images than in STIR-FSE images in the SDFT (Schramme et al., 2010; Karlin et al., 2011; Berner et al., 2016; Berner, 2017; Berner et al., 2020).

High-field MRI

Most high-field MRI systems with a field strength of 1 Tesla (T) and above are installed in larger referral centres. Examination is usually performed in a closed-bore magnet and requires the horse to be anaesthetised (Lutter et al., 2015). Due to the higher signal-to-noise ratio and corresponding increased image contrast and resolution, the tendon margins are better defined, and subtle lesions appear more conspicuous on high-field MR images when compared to standing low-field MRI (Ghazinoor et al., 2007; Murray et al., 2009). Whilst tendon lesions and adhesions are generally detected on low- and high-field MR images, small focal lesions ($\leq$ 1 mm in diameter) and subtle dorsal fibrillation of the DDFT may be visible on high-field MRI only (Murray et al., 2009).

'Magic angle MRI'

Similar to the appearance on low-field MRI where the B_0 magnetic field is oriented vertically, the 'magic angle' effect at the distal aspect of the DDFT can be recognised mainly on T1-weighted high-field MR images, when the long axis of the tendon is oriented at approximately 55° (+/- 5-7°) to the horizontally oriented static magnetic field (Busoni and Snaps, 2002; Spriet and McKnight, 2009; Werpy et al., 2010). The artefact is characterised by a hyperintense signal and can impact on the interpretation of MR images (Erickson et al., 1991; Erickson et al., 1993). Since tendons generally present with little to no signal on MR images, the intentional application of the 'magic angle' effect has been proposed to further investigate the available signal of the tendon structure. The so called 'magic angle MRI' allows sufficient signal to be obtained using the standard pulse sequences of clinical MRI systems (Bydder et al., 2007). Using this technique, an increased T1 relaxation time has been reported in cases of chronic Achilles tendinopathy in humans (Marshall et al., 2002; Oatridge et al., 2003).

In an initial 'magic angle MRI' study on equine specimens, reference values for the normal T1 relaxation times of the equine SDFT, DDFT and suspensory ligament were determined (Spriet et al., 2011). To further assess possible changes in T1 relaxation associated with tendinopathy, both laser-induced and naturally occurring SDFT lesions were subsequently evaluated (Spriet et al., 2012). All naturally occurring lesions were visible on conventional as well as on 'magic angle' MR images. Based on the histological findings the authors state however, that 'magic angle MRI' might be advantageous for the identification of diffuse changes in tendon composition, that appeared hypointense on conventional MR imaging (Spriet et al., 2012). Whilst the feasibility of 'magic angle MRI' has been

demonstrated in high-and low-field MRI systems, the adequate positioning of the limb may still prove to be a challenge in an *in vivo* setting (Spriet et al., 2012; Horstmeier et al., 2019).

Influence of local injection on MRI interpretation

Research assessing the influence of diagnostic analgesia on MR image interpretation showed that perineural analgesia of the palmar digital nerves, as well as intra-synovial analgesia of the navicular bursa and the distal interphalangeal joint, do not significantly alter MR images of the distal limb at 1.5 T (Black et al., 2013). Only the injection of 15 ml mepivacaine into the digital flexor tendon sheath caused an iatrogenic increase in synovial fluid volume as detected on MRI at 24 and 72 hours post injection (Black et al., 2013). The study additionally described that needle tracts could not be appreciated consistently at any injection site apart from the site of the navicular bursa injection, where some evidence for a needle tract was detected in 10/15 limbs at 72 hours post injection.

Another study further investigated the influence of saline injection (30-35 ml) into the digital flexor tendon sheath for the purpose of enhanced ultrasonographic and 1.5 T high-field MR image interpretation (Daniel et al., 2019). The study showed that the presence of fluid significantly improved the delineation of the DDFT in both imaging modalities and the visualisation of the margins of the SDFT on MR images. As the technique did not introduce any artefacts or altered the dimensions of the intra-thecal structures, further evaluation in clinical cases should be of value particularly for the detection of marginal tendon lesions. It is however important to consider that patients might be reluctant to stand during low-field MRI following distention of the digital flexor tendon sheath. Consequently, the technique appears to be more suited for high-field MR evaluation.

In order to facilitate assessment of the dorsal border of the DDFT at the level of the navicular bone, the injection of the navicular bursa with saline (6-10 ml) or a mixture of saline and contrast medium (5-6 ml, 1:1 ratio of 0.9% saline: Diatrizoate Meglumine and Diatrizoate Sodium; Hypaque-76®) has been proposed (Schramme et al., 2009; Maher et al., 2011). The distension of the navicular bursa physically separates the palmar surface of the navicular bone from the dorsal margin of the DDFT and allows adhesions, DDFT fibrillation and tendon splits at this level to be recognized more readily. The limitations of the technique include the time required for the navicular bursa injection under radiographic guidance, and the risk of rupture of the navicular bursa, especially if a volume in excess of 5 ml is injected (Schramme et al., 2009; Maher et al., 2011). Alternatively, the distension of the distal interphalangeal joint with saline (20-35 ml) alters the position of the proximal recess of the navicular bursa and enhances the visualisation of the dorsal border of the DDFT, similar to the direct approach to the navicular bursa (McGill et al., 2015). Both techniques are described to be more reliable in the non-weightbearing limb when no pressure is exerted between the navicular bone and the DDFT and are therefore probably more suitable for high-field MRI *in vivo* (Maher et al., 2011; McGill et al., 2015).

Contrast-enhanced MRI

Gadolinium-based contrast-enhanced MRI is routinely performed for human and small animal neurologic, oncologic and vascular imaging (Owen, 2018; Scott, 2018). Gadolinium shortens the relaxation time constants (T1 and T2) of the tissues, which leads to an increase in signal intensity, especially in T1-weighted images (Lin and Brown, 2007). First clinical reports recommended an intra-venous gadopentate dimeglumine dose of 0.1 ml/kg (50 ml/horse) for musculoskeletal contrast-enhanced MRI in horses (Judy et al., 2008; Saveraid and Judy, 2012; Daniel et al., 2013). The authors described the potential for an

improved recognition and assessment of tendon lesions, similar to the human Achilles tendon, where a correlation between contrast enhancement and the severity of tendon lesions has been demonstrated in a number of clinical cases (Shalabi et al., 2002; Richards et al., 2010).

In order to decrease the volume and associated expense of gadolinium required for contrast-enhanced MRI in horses, regional limb perfusion with gadopentate dimeglumine (5 ml in 5 ml 0.9% saline) via the palmar/plantar digital vein at the level of the mid metacarpus/metatarsus was evaluated in a prospective clinical study (Aarsvold et al., 2018). Pre- and post-contrast high-field (1.5 T) MRI was performed in anaesthetized horses in lateral recumbency. Contrast enhancement in the distal limb was adequate provided the tourniquet was secured in place. Multiple lesions were identified and were mostly visible on pre-contrast as well as contrast-enhanced MR images. The authors describe, however, that the technique aids the characterisation of lesions including adhesions and neovascularisation of the DDFT (Aarsvold et al., 2018). In the standing horse the approach may be limited due to difficulties in ensuring patients stand still for the requisite amount of time for the examination post tourniquet application. Additionally, it might be challenging to replicate the exact position of the foot in the magnet pre- and post contrast injection.

A further study compared systemic intra-venous injection with regional intra-arterial injection of gadolinium in a group of horses with lameness localized to the foot (De Zani et al., 2018). The injection of 0.02 ml/kg of gadolinium in the radial artery resulted in a higher ratio of MRI contrast enhancement when compared to the systemic intra-venous route (0.1 ml/kg). Whilst the tendon tissue appeared generally not highly vascularised, significant

enhancement of the DDFT and peritendinous tissue was noted in the area of suspected pathological lesions (De Zani et al., 2018).

The contrast enhancement in association with tendinopathy is most likely related to an increased capillary permeability and diffusion of blood into the interstitial space in the acute stages of the injury. Additionally, neovascularisation and granulation tissue formation are suspected to show increased contrast uptake. However, histological studies of contrast-enhancing lesion in the equine distal limb are currently lacking (Shalabi et al., 2002; Saveraid and Judy, 2012; Nelson et al., 2017).

Side effects of the administration of gadolinium-based contrast agents are described in human and small animal patients, but no severe adverse reactions were encountered in the aforementioned equine studies (Wible et al., 2001; Grobner and Prischl, 2007; Lin and Brown, 2007; Girard and Leece, 2010; Saveraid and Judy, 2012; Prince et al., 2017; Aarsvold et al., 2018; De Zani et al., 2018). A recent review of the use of contrast media in horses classified the risk associated with the administration of gadolinium generally as low, provided horses do not suffer underlying renal disease or dehydration (Nelson et al., 2017). Future research should further ascertain the benefits of contrast-enhanced over standard MRI for the assessment of tendon lesions and identify how imaging findings correlate with histopathology. Additionally, the combined approach of contrast-enhanced and ‘magic angle MRI’ as described for the human Achilles tendon might be of interest for equine flexor tendon imaging (Marshall et al., 2002).

Ultra-high field MRI

The high-field MRI systems currently installed in veterinary centres for clinical applications operate at a field strength of 1.5 to 3 T. Magnets used in humans for clinical purposes have now reached 7 T, and preclinical research ultra-high field MRI systems exceeding a field strength of 10 T are available (Alizai et al., 2018; Ladd et al., 2018).

Low- and high-field MRI facilitates the detection and assessment of tendon lesions, but the visualisation of the tendon structure remains difficult. The very short transverse relaxation time of normal tendon tissue, with the relatively long echo times used in conventional clinical MRI sequences usually result in the complete decay of tendon signal before it can be sampled (Juras et al., 2012; Guidetti et al., 2018; Juras et al., 2019). With increasing field strength and signal-to-noise ratio, and the use of ultrashort echo time (UTE) and other sequences, MR images of the finer tendon structural components can be obtained (Fig. 2) (Robson et al., 2004; Du et al., 2010; Moser et al., 2012; Juras et al., 2013; Chang et al., 2015; Foure, 2016). In man, ultra-high field MRI is utilized to visualise the fascicular pattern of the Achilles tendon *in vivo* (Han et al., 2014; Foure, 2016; Juras et al., 2019).

Ultra-high field MRI of the equine SDFT

Ultra-high field MRI (9.4 T) of the equine SDFT facilitates the detailed assessment of the tendon structure with clear delineation of the tendon fascicles and interfascicular matrix (Fig. 2 A + B). Additionally, T2*-weighted 3D-FISP gradient echo transverse images provide a comprehensive picture for the characterisation of tendon lesions (Fig. 2C). At this stage the size of the radiofrequency coil and the time required to obtain this high level of anatomical detail preclude the *in vivo* assessment of tendon lesions in horses. The cost and technical expertise involved with MR imaging at higher field strength limits its availability in

veterinary medicine, however, ultra-high field MRI offers promising prospects for musculoskeletal imaging as clinical progress continues (Alizai et al., 2018; Ladd et al., 2018).

Computed tomography

The limited availability of MRI has led to the investigation of alternative modalities for soft tissue advanced diagnostic imaging in equine orthopaedics (Tucker and Sande, 2001; Puchalski, 2012; Jones et al., 2019). A study comparing MRI and CT for the assessment of the equine distal limb found similar scores for the visibility of the DDFT in the area of the pastern for both modalities, but the distal DDFT at the level of insertion showed better visualisation scores with low-field MRI (Vallance et al., 2012a). Likewise, the classification of DDFT lesions varies depending on the imaging modality used for interpretation. More lesions of the distal DDFT were detected with low-field MRI but lesions at the level of the pastern as well as abrasions and mineralisation of the DDFT were more likely to be diagnosed with CT in a cohort of clinical cases (Fig. 3) (Vallance et al., 2012b). Additional reports comparing both, MRI and CT imaging findings of the same subject with results of histopathological examination would give further insight and support image interpretation (Whitton et al., 1998; Puchalski et al., 2009).

Contrast-enhanced computed tomography

The contrast media used for CT studies in equine patients are usually iodinated solutions that strongly attenuate X-rays and highlight areas of increased vascular perfusion or permeability (Bushberg et al., 2012; Nelson et al., 2017). Following acquisition of pre-contrast images the intra-vascular or intra-thecal route of administration may be chosen for contrast-enhanced CT imaging of the equine distal limb (Puchalski, 2012; Nelson et al., 2017).

There are some reports of intra-venous contrast studies in the horse (Hunter et al., 2016; Walker et al., 2017). However, the technique most commonly described is the regional intra-arterial injection of contrast medium, including placement of a catheter in the medial palmar artery at the level of the carpometacarpal joint under ultrasonographic guidance in the anaesthetised horse. Steady-state infusion of a 1:1 dilution of ionic-iodinated contrast in saline is subsequently maintained with a remotely controlled pressure injector (2 ml/s), starting 3-5 seconds prior to CT examination (Collins et al., 2004; Puchalski et al., 2005; Puchalski et al., 2007; Puchalski et al., 2009; Pollard and Puchalski, 2011b). Whilst tendon lesions are less common in the hindlimb, contrast application via catheterisation of the lateral dorsal metatarsal artery is also described (van Hamel et al., 2014) (Fig. 4). The normal CT anatomy and attenuation values for tendon and ligament before and after intra-arterial contrast administration have been documented in detail (Tietje et al., 2001; Puchalski et al., 2007; Vallance et al., 2012a; Claerhoudt et al., 2014). The DDFT generally shows a slight but significant increase in post-contrast attenuation (8-17 HU) that potentially impairs on the clear anatomical visualisation of the tendon (Puchalski et al., 2007; Vallance et al., 2012a).

DDFT lesions in the area of the foot are usually characterised by marked contrast enhancement (> 20 HU) that may be central, peripheral or diffuse (Puchalski et al., 2009; Puchalski, 2011; Vallance et al., 2012b; van Hamel et al., 2014). Lack of contrast enhancement has been occasionally observed in dorsal border lesions of the DDFT. A sensitivity of 93% for lesion detection was determined following histopathological examination of the affected tissue in one study (van Hamel et al., 2014). All false negative results obtained in this study were at the level of the navicular bone where the visibility of the DDFT is most limited on CT images (Vallance et al., 2012a; van Hamel et al., 2014). Clinical

studies have shown that lesions of the DDFT can also be diagnosed based on non-contrast-enhanced CT (Tietje et al., 2001; Jones et al., 2019). However, lesions in the area of the DDFT insertion were more likely to be identified post-contrast in one study (Vallance et al., 2012b).

CT contrast tenography may aid the evaluation of the flexor tendons as they course through the digital flexor tendon sheath (Fig. 5). Consistent delineation of the flexor tendon borders and the *manica flexoria* has been described after intra-thecal injection of nonionic-iodinated contrast solution (60 ml) into the digital flexor tendon sheath of cadaver limbs without flexor tendon pathology (Lacitignola et al., 2015; Agass et al., 2018). Further research should confirm the value of this technique for diagnostic purposes and pre-surgical planning.

Adverse reactions to the intravascular administration of iodinated contrast are rare in horses but may include a transient increase in heart rate and blood pressure as well as local or generalised skin reactions (Gunkel et al., 2004; Pollard and Puchalski, 2011a; Nelson et al., 2017). CT technology is advancing rapidly and the resolution of images obtained for the assessment of clinical cases has considerably increased over the past decade (Puchalski, 2012; Riggs, 2018). High slice number multidetector CT scanners are becoming more widely available and first examples of distal limb examination in standing horses have been reported (Desbrosse et al., 2008; Koch et al., 2020; Mageed 2020; Pauwels et al., 2021). In contrast to MR imaging CT does not offer the capability of accurately detecting the fluid content within a tendon lesion to date. However, with its improved image quality and fast acquisition time, CT may provide a practical alternative to MRI for advanced diagnostic imaging of the equine flexor tendons (Riggs, 2018; Jones et al., 2019). Future research should show whether CT

imaging is comparable to MRI regarding the assessment of lesion progression over time. Additionally, patient tolerance regarding contrast procedures in the standing horse warrants further investigation.

Positron emission tomography

Positron Emission tomography (PET) is a nuclear medicine imaging technique mainly used in the field of human oncology, but orthopaedic applications are also described in man (Fischer et al., 2010; Fischer, 2013; Kim et al., 2015; Eliasson et al., 2016; Aide et al., 2019). In contrast to gamma scintigraphy where planar images are obtained after the injection of a radioactive agent, PET acquires cross-sectional images allowing for three-dimensional assessment of the region of interest (Spriet, 2019). PET is usually combined with CT in order to obtain functional and structural information. As this setup is currently difficult to realise in large patients like horses, a PET scanner used for preclinical brain research has been adapted for PET imaging of the equine distal limb. First reports of PET imaging in equine orthopaedics mainly describe the benefits of the technique for the detection of osseous lesions and enthesopathy (Spriet et al., 2016; Spriet et al., 2018; Spriet et al., 2019; Norvall et al., 2020). PET imaging has been applied for the monitoring of the healing response after Achilles tendon rupture in human patients and increased uptake of the glucose tracer ^{18}F-fluorodeoxyglucose was detected in horses with SDFT and DDFT tendinopathy in one exploratory study (Eliasson et al., 2016; Spriet et al., 2016). Future studies will further determine the value of PET imaging for the assessment of the equine flexor tendons in clinical cases (Spriet, 2019).

Conclusion

The rapid and ongoing technological progress and particularly the influence of modern computing has led to the development of a multitude of approaches for soft tissue imaging. Not all techniques described in preclinical studies or human orthopaedic research will be economical or practical enough to be carried through into veterinary clinical diagnostics. However, the last two decades have shown how fast advanced diagnostic imaging modalities including MRI and CT have been integrated in equine orthopaedics at referral level. Both modalities have benefits and disadvantages, particularly for the assessment of flexor tendon injuries. Detailed knowledge of MRI and CT approaches including the implications of the 'magic angle' and the use of injection techniques and contrast should aid image interpretation and selection of the appropriate modality. As diagnostic imaging is crucial for the diagnosis and monitoring of equine tendinopathy and potentially aids the prevention of tendon injury, there is ongoing demand for future studies in this developing field of research.

Conflict of intertest statement

None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of the paper.

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Table 1

Overview of the literature validating magnetic resonance imaging (MRI) in the equine distal limb for the assessment of the superficial digital flexor tendon (SDFT) and the deep digital flexor tendon (DDFT).

Low-field MRI	Literature source	Area examined	No of horses
0.2 T	Kasashima et al., 2002	SDFT	6
0.27 T	Murray et al. 2009	SDFT / DDFT	10
0.25 T	Karlin et al., 2011	SDFT	8
0.27 T	Sherlock et al., 2015	DDFT	26
High-field MRI			
1.5 T	Murray et al., 2004	DDFT (distal)	38
1.5 T	Murray et al., 2006a	DDFT (distal)	32
1.5 T	Murray et al., 2006b	DDFT (distal)	34
1.5 T	Murray et al., 2009	SDFT / DDFT	10
1.5 T	Blunden et al., 2006	DDFT (distal)	32
1.5 T	Blunden et al., 2009	DDFT (distal)	46

915 **Figure legends**

916 Fig 1. T1-weighted gradient echo (GRE) FAST transverse low-field (0.27T) magnetic
917 resonance image of the equine distal limb at proximal pastern level (lateral is to the left). (A)
918 Note the increased T2 signal intense 'magic angle' artefact at the mid- to lateral aspect of the
919 superficial digital flexor tendon (SDFT) (black arrow) as observed with 'leaning in' or lateral
920 rotation of the limb during image acquisition. (B) lesion of the medial lobe of the SDFT
921 (white arrow) (Image courtesy of Birte Drees, Lucidity Diagnostics 2020).

922

923 Fig. 2. T2*-weighted 3D-FISP (fast imaging with steady-state free precession) gradient echo
924 transverse MR images of the superficial digital flexor tendon (lateral is to the left). (A) 3-year
925 old Irish Sports Horse mare without pre-existing orthopaedic condition. (B) 25-year old
926 Thoroughbred mare without a history of orthopaedic disease. Thinning of the interfascicular
927 matrix is evident as a result of ageing. (C) 8-year old Thoroughbred gelding with clinical SDFT
928 tendinopathy.

929

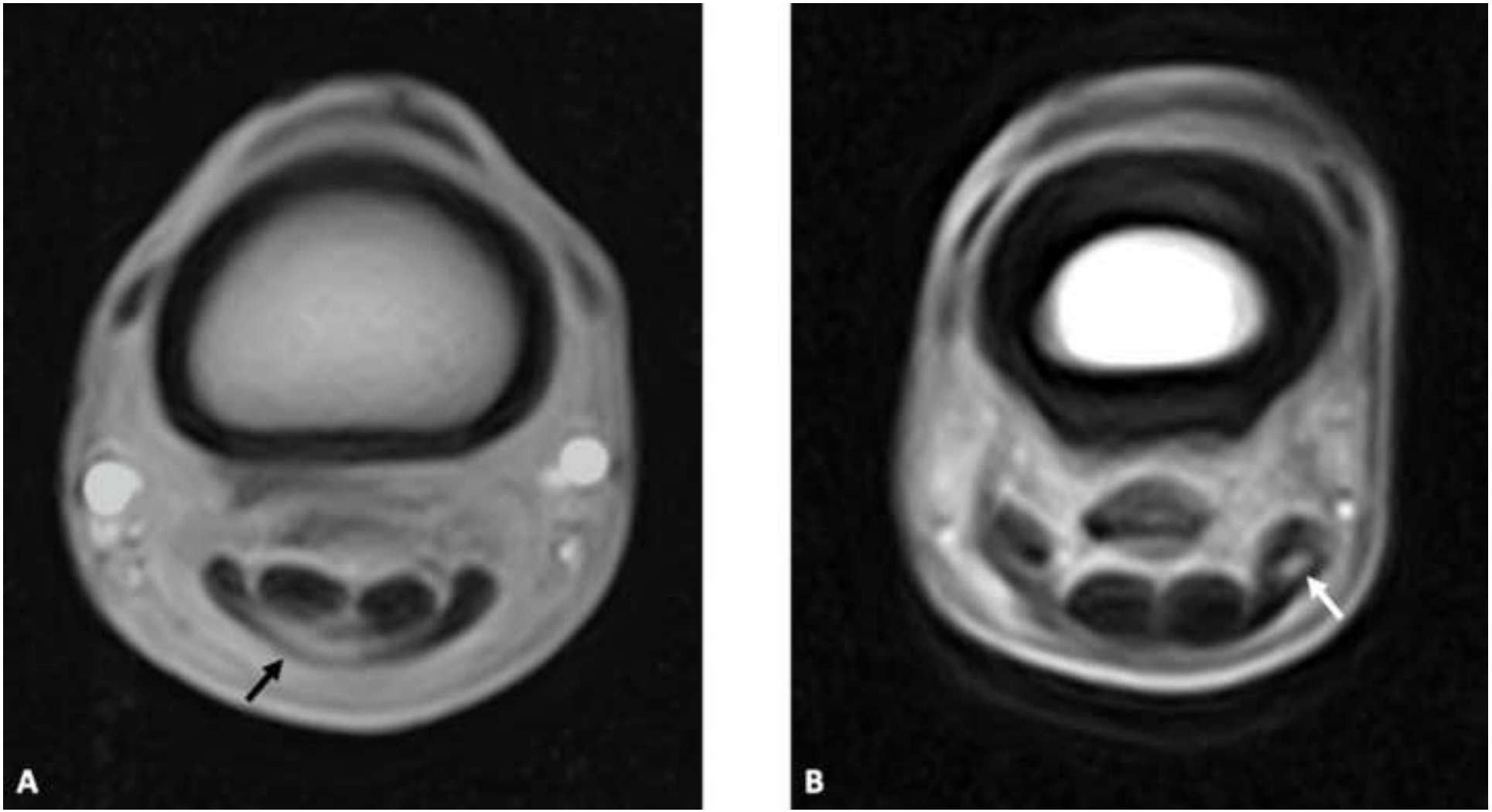
930 Fig. 3. Transverse computed tomographic (CT) images (soft tissue window without contrast)
931 of the deep digital flexor tendon (DDFT) at the level of the lower pastern (lateral is to the
932 left). (A) Longitudinal split of the lateral lobe of the DDFT (white arrow) with moderate
933 distension of the navicular bursa (black arrow). (B) Dorsal border lesion of the DDFT (white
934 arrow) (Images courtesy of Carolin Müller, Lucidity Diagnostics 2020).

935

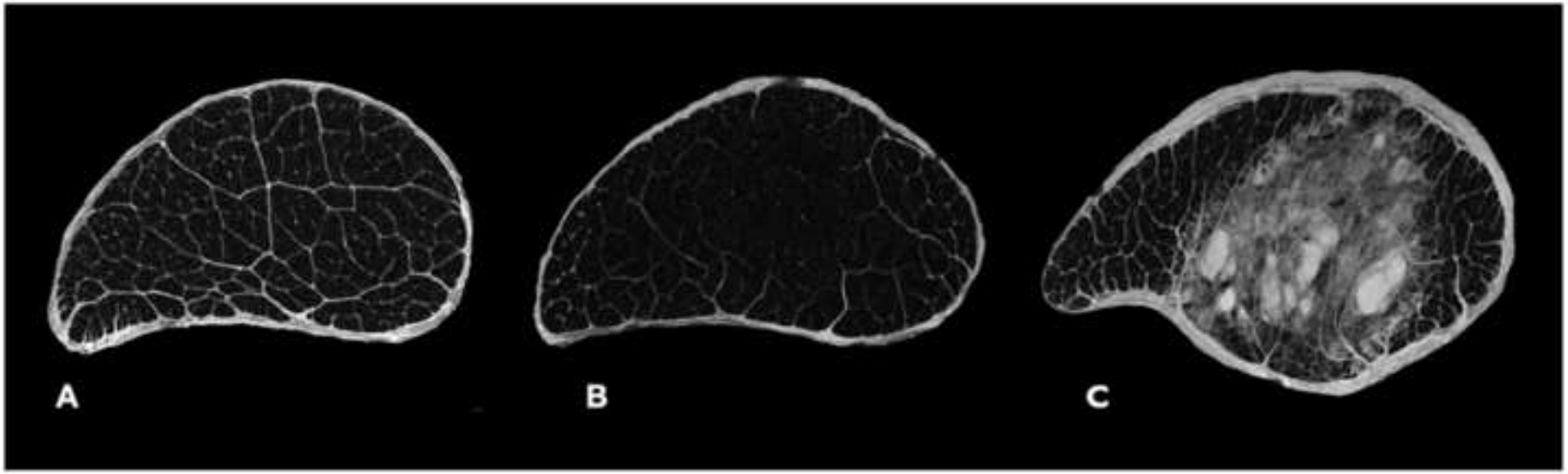
936 Fig. 4. Contrast enhanced computed tomographic images (bone window) showing the deep
937 digital flexor tendon (DDFT) of the left hindlimb of a 10-year-old Warmblood showjumper,
938 acquired during steady-state infusion of ionic-iodinated contrast in saline (1:1; 2ml/s) via the
939 lateral dorsal metatarsal artery (lateral is to the left). (A) Note the increased contrast

940 enhancement associated with a core lesion of the DDFT in zone 4B (white arrow). (B)
941 Additionally, perilesional contrast attenuation was evident in both lobes of the DDFT in zone
942 P2A (white arrows) in the same horse.
943
944 Fig. 5. Computed tomographic (CT) images of the flexor tendons at the level of the digital
945 flexor tendon sheath with (B + D) and without (A + C) intra-thecal application of nonionic-
946 iodinated contrast. The superficial and deep digital flexor tendons can be recognized on
947 transverse (A) and sagittal (C) CT images using the soft tissue window. The outline of the
948 *manica flexoria* (white arrow) and the flexor tendons is highlighted following injection of the
949 digital flexor tendon sheath with contrast (B + D) (lateral is to the left on Fig. 5 A and B)
950 (Images courtesy of Carolin Müller, Lucidity Diagnostics 2020).

Figure



Figure



Figure

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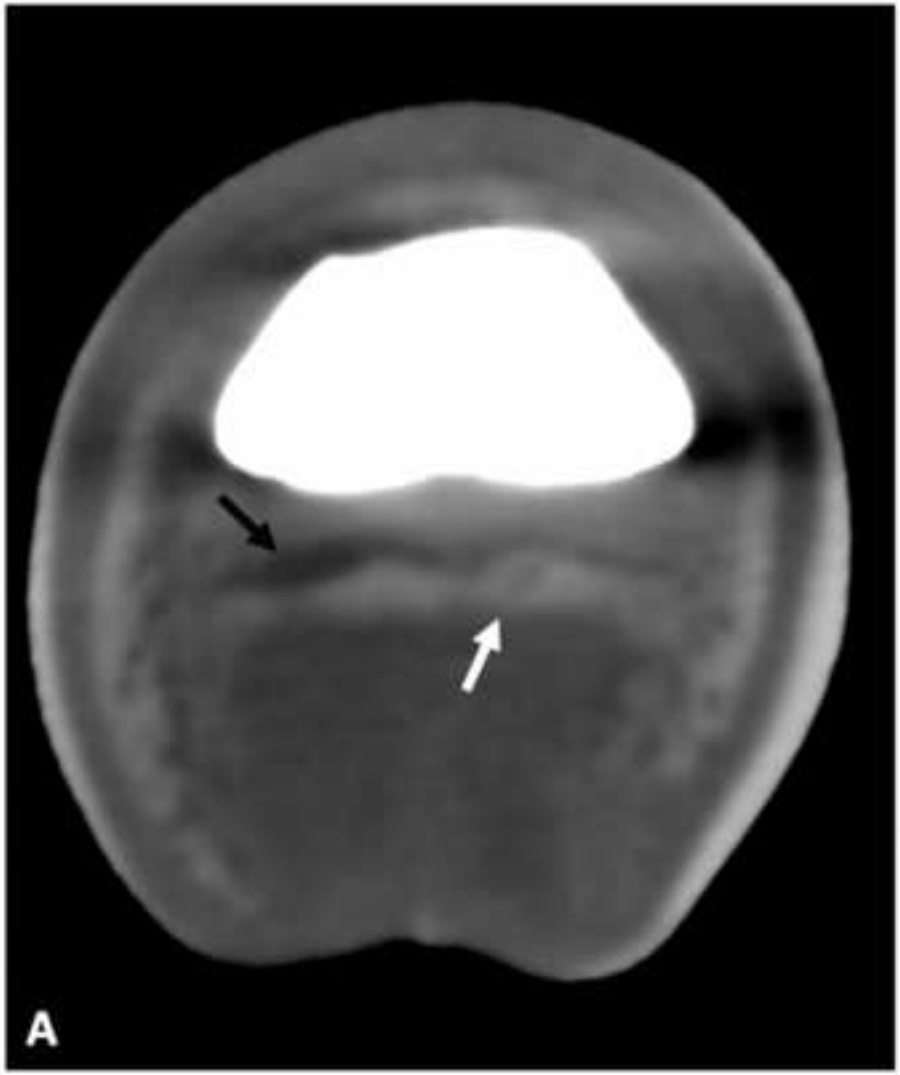
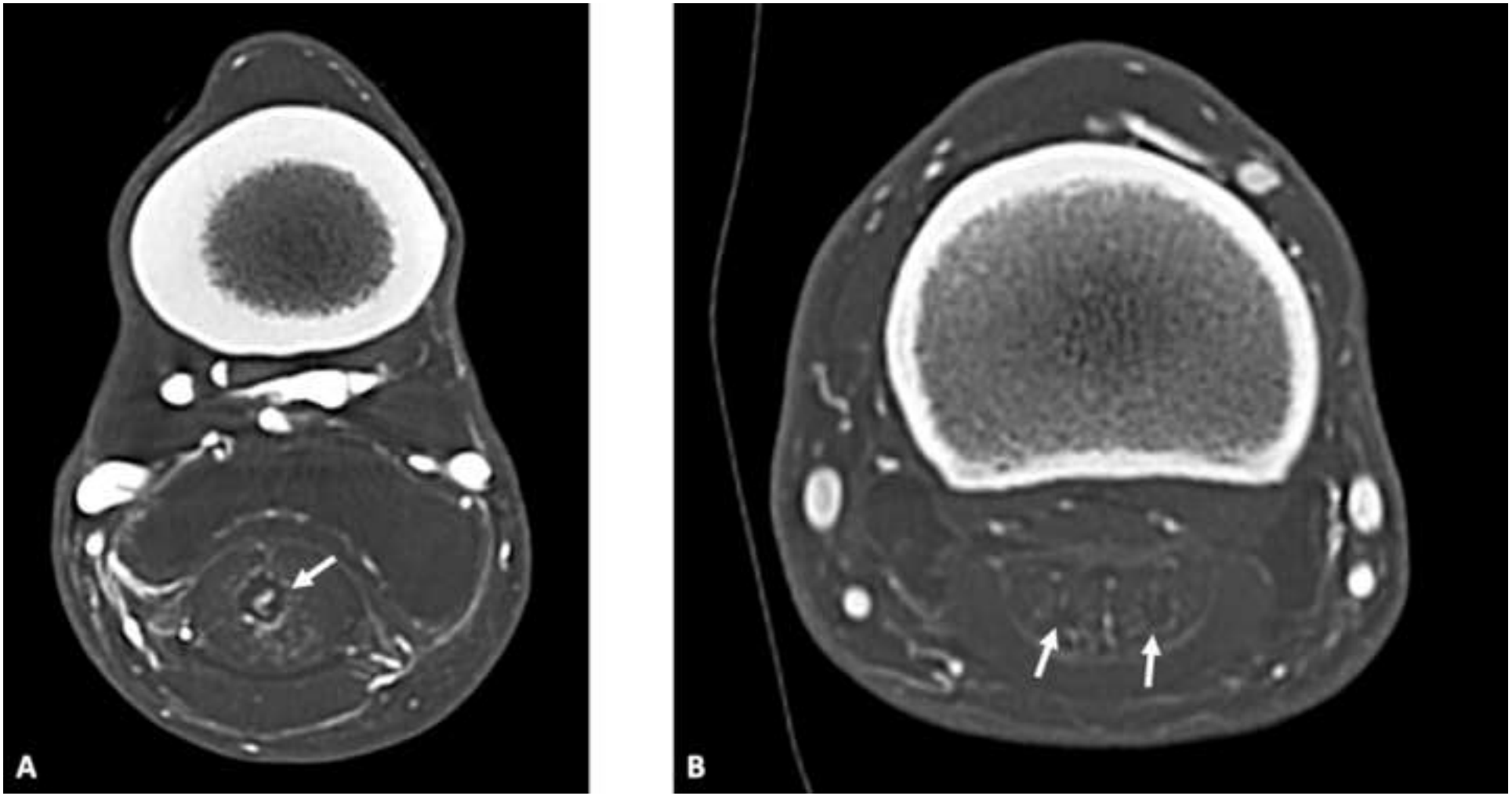


Figure



Figure

Highlights review part 2 – advanced diagnostic imaging

- The magic angle and the use of contrast may enhance flexor tendon Magnetic Resonance Imaging (MRI)
- Computed tomography finds wider use in equine orthopaedic soft tissue imaging
- Positron emission tomography and ultra-high field MRI provide future prospect is tendon imaging

Revision note – tendon imaging review part 2

The authors would like to thank the reviewers for their valuable comments and suggestions concerning the manuscript 'Equine flexor tendon imaging part 2 – current status and future directions in advanced diagnostic imaging'.
The manuscript has been revised accordingly and the authors' response is detailed below. Changes to the manuscript are highlighted as track changes (reviewing mode). The authors hope that the amended manuscript will satisfy the reviewers concerns and is now considered suitable for publication.

Reviewer #1

Reviewer comment: A very well-written, concise and informative summary of the currently available advanced imaging technology for assessment of tendon pathology. Overall part 2 is written in a slightly more clinically relevant and engaging manner than part 1, with more information regarding the clinical applications of the various technologies and their sensitivity and specificity for lesion detection. I acknowledge that this likely reflects both the authors' experience and the greater wealth of literature available for these modalities. Again, further images would be appreciated, especially in highlighting the utility of contrast enhanced CT in detection of DDFT lesions within the foot as well as examples of lesions of the DDFT and SDFT on low field and high field MRI.

Authors' response: The authors would like to thank reviewer 1 for the kind words. Additional images were added as requested (Figure 1 + 4).

Reviewer comment: Lines 102-107 - The reported prognoses for lesions in the Cillan-Garcia study are accurate, and reflect return to ridden exercise, however I feel that the authors should make clear that these figures do not reflect the proportion of horses that returned to their previous level of exercise, which were much lower. The effect of lesion location should also be included, as insertional lesions had a worse prognosis than lesions in the region of the navicular bone and navicular bursa.

Authors' response: The authors agree and have changed the paragraph as requested to state the results of the cited study more accurately (lines126-131).

Reviewer comment: Lines 171-177 - Would it be prudent for the authors to mention that these techniques were performed in high field magnets only, and that the technique would be difficult in standing magnet as patient would likely be reluctant to stand following distention of the sheath?

Authors' response: In clinical practice the authors frequently perform distention of the digital flexor tendon sheath prior to ultrasonographic evaluation where a mix of radiopaque contrast and local anaesthetic is injected intra-thecally. Contrast radiography and assessment of the block is

subsequently performed, followed by ultrasonographic evaluation. We hardly ever encounter problems with horses that would not stand still for ultrasonographic evaluation with some sedation. However, things might be different in the magnet and we usually do not use more than 25mls in total. The sentence was therefore changed as requested (lines 206-207 and 211-214).

Reviewer comment: Lines 208-216 - again it may be prudent to mention that this approach may be limited in the standing horse due to difficulties in ensuring patients stand still for the requisite amount of time for the examination post tourniquet application as well as difficulties in replicating the positioning of the foot pre and post contrast injection.

Authors' response: The authors would like to thank Reviewer 1 for this valid and practical consideration. The paragraph was changed accordingly (lines 251-252 and 256-259).

Reviewer comment: Lines 297-301 - The approach described is for the forelimb only. Although DDFT lesions are less common in the hindlimb, they are documented to occur. Would it be feasible to add details for intra-arterial contrast in the HL also?

Authors' response: Details about intra-arterial contrast CT in the hindlimb were added to the paragraph (lines 349-351 and Figure 4).

Reviewer comment: Additionally, it is not clear from the manuscript that the recommended protocol would be to acquire pre-contrast images followed by contrast enhanced images on CT. It may be useful to the reader to add a line detailing this.

Authors' response: It is now pointed out in the manuscript that contrast enhanced CT is performed following acquisition of pre-contrast images (lines 336-337).

Reviewer comment: Lines 338-340 - Whilst I agree that the advantages in acquisition time and image resolution due to the availability of thinner slices and reconstructions in different algorithms make CT an attractive prospect for tendon imaging, the additional information on fluid content of tendon lesions on MRI images should not be overlooked. Insufficient work has been performed looking at the progression of lesions over time on CT imaging when compared to MRI. Similarly there is little work looking at the use of contrast procedures in the standing systems. It is my suspicion that intra-arterial contrast may be poorly tolerated in the standing sedated patient.

Authors' response: The authors agree with the mentioned concerns of Reviewer 1 and the paragraph was adjust as requested (lines 386-395).

Reviewer comment: From a practice management/business perspective, the rise in popularity of standing MRI systems has in part been due to the business model of the manufacturer making

these systems affordable with minimal capital outlay (compared with outright purchase of a unit). Additionally, the ability to image under standing sedation and thus avoiding the risks inherent with general anaesthesia has been key to the acceptance of this imaging modality within the horse-owning community. Unless similar business models were to be put in place for standing CT units it is difficult to imagine a similar rapid growth in popularity and availability.

Authors' response: The authors appreciate the reviewer's thought and also believe that it will take years for CT imaging to become as established as MRI for the assessment of orthopaedic conditions in horses. Business models similar to that of Hallmarq where standing examination of the distal limb is possible and the CT unit does not need to be purchased in total are however on the market and appear to be selling well (example Qalibra (Vet-DICon) so far mainly in Europe, UK, Australia and the US, Mageed EVE 2020, line 386).

Mageed, M., 2020. Standing computed tomography of the equine limb using a multi-slice helical scanner: Technique and feasibility study. Equine Veterinary Education, (Epub ahead of print) doi: 10.1111/eve.13388

Reviewer #2:

Reviewer comment: This manuscript is an accurate representation of a large body of literature assessing advanced imaging of equine tendon. This is a useful review and the authors should be commended for the amount of work put in this manuscript.
I only have one specific comment, regarding a correction needed in the description of the magic angle effect.
L.68-69: "increased T2 signal". This statement regarding the magic angle effect is misleading. The magic angle effect leads to an increase of the T2 relaxation time, which results in increase signal intensity in sequences with short Echo Time (TE), ie T1 weighted and PD sequences (As mentioned L.73-74). Typically, the magic angle effect is not apparent on T2 weighted sequences, which is an important fact to help distinguish between the artifact and an actual lesion.

Authors' response: The authors would like to thank reviewer 2 for the kind words and for the correction. The sentences were adjusted accordingly (lines 83 and 86-87).

Reviewer #3:

Reviewer comment: There are two papers titled Parts 1 and 2 but they don't really hang together, because one focuses on the metacarpal region and the other (this one) focuses on the DDFT and the digit. They should be completely separate and the title of this paper should more accurately reflect its content.
I expected to find information relevant to the SDFT and while this is mentioned in passing, the paper focusses on the DDFT.

Authors' response: The authors appreciate the reviewers concern, and the title of both parts was adjusted to address the issue and state the content of the manuscripts more precisely (lines 3-4).

Reviewer comment: 'Besides lesion detection, future developments in tendon imaging focus on gaining enhanced structural and functional information about the tendon architecture with the prospect to prevent injury.' - Have you really presented any information to support this statement?

Authors' response: The authors agree, review part one is more focused on the functional assessment and review part two more on structural information. The sentence in the abstract was altered accordingly (lines 28-30).

Reviewer comment: Line 34 tendon repeats a word in the Title; key words aim to provide additional words for a search engine.

Authors' response: The keyword 'Tendon' was replaced with 'Tendinopathy' (line 34).

Reviewer comment: The Introduction implies that magic angle MRI is a useful technique whereas the magic angle effect is a term used to describe annoying artefacts which hinder interpretation, as illustrated in Figure 1. I know of no-one using this technique to enhance diagnosis in the equine field, although there are some theoretical ideas about it.
I think the method of searching the literature needs to be described without reliance on the other paper.

Authors' response: The statement about the 'magic angle' in the abstract was altered to ensure that it does not imply any information considering the usefulness of 'magic angle' MRI (lines 27-28). Additional details regarding the literature search were added to the introduction (lines 56-59).

Reviewer comment: Line 41 podotrochlear apparatus would be better terminology than navicular apparatus.
I would suggest that 'and palmar foot pain' is redundant.

Authors' response: The authors agree and the sentence was altered as requested (line 46).

Reviewer comment: Line 55 I don't think that you can say that low-field MRI is the gold standard; high field MRI is infinitely superior.

Authors' response: The authors agree and the sentence was altered accordingly (line 63).

Reviewer comment: *The initial validation comparing histology and MRI was done using high-field MRI.*
Line 58 1 Tesla is not low-field!

Authors' response: The heading of the paragraph was adjusted to indicate that it is meant to be a more general introduction to MR imaging (line 61). It is indicated in lines 72-74 that the initial validation was performed using high-field MRI.

Reviewer comment: *Please make sure that you separate which references relate to low-field and which to high-field and that the reader gets an idea of the numbers of horses and the areas examined in the studies cited - perhaps in Table form.*

Authors' response: A table including the requested details was added (Table 1).

Reviewer comment: *Part 1 focussed on the metacarpal region - I am curious why this review is extended not only to the DDFT in the hoof capsule, but also those injuries sustained as the result of penetrating injuries.*
The use of ultrasonography in the assessment of these lesions has not been discussed. In a 2-part paper of this type I would expect the general anatomical areas under review to be largely the same.
There are numerous references available that discuss the uses and limitations of ultrasonography for evaluation of structures in the digit. This review does not appear to be balanced in its coverage.

Authors' response: The authors agree, review part 1 and part 2 are not balanced regarding the anatomical region discussed. A systematic review assessing the recent literature about flexor tendon imaging was performed without specific focus on the SDFT or the DDFT or the respective level/anatomic region of the tendon within the limb. It is however not a surprise that there is more literature available describing ultrasonographic techniques for the SDFT in the metacarpal region, and for advanced diagnostic imaging techniques of the DDFT at the level of the foot. The tendon each manuscript is focused on is therefore now stated in the title of both parts of the review to prevent confusion.
The literature describing ultrasonographic techniques for the assessment of the DDFT within the foot is particularly valuable for cases where advanced diagnostic imaging is not available or there are financial constraints. The authors however feel that ultrasonography of the foot is not exactly a future trend in equine flexor tendon imaging, and it was therefore not in the focus of the current investigation.
Depending on their exact location, foot penetrations can lead to severe injury of the DDFT and associated structures and the advantages of MRI for their diagnosis is a recent development. Whilst the authors agree that this information goes slightly beyond the scope of the review, we decided to mention the literature describing MR imaging of this particular aspect as it is considered to provide relevant and practical information for the reader and indicates a useful applications of MR imaging.

Reviewer comment: Lines 68-8 What is meant by T2 signal?
You go on to say that the MAE is seen in T1W images
This review is supposed to be about flexor tendon injuries so why are you talking about CL injuries of the DIP joint. Please stick to the subject! MAE is not a big problem with the flexor tendons. Put this into proper perspective. This whole section seems to reflect a lack of understanding of the MAE.

Authors' response: The authors apologise for the use of confusing terminology. The artefact is characterised by increased T2 relaxation time and this has been corrected (line 83). The information concerning the collateral ligaments of the distal interphalangeal joint was removed from the sentence (line 90).

Reviewer comment: Lines 86-95 I do not think that this section represents an accurate overview of the literature. Check which studies actually are longitudinal studies - not all of them are!

Authors' response: The studies that did not include repeated MRI examination were removed from the paragraph (line 118).

Reviewer comment: Line 97 The term 'development' is not appropriate here - I think you are referring to the evolution of lesions over time after diagnosis.

Authors' response: The term 'evolution' was included (line 120).

Reviewer comment: Lines 100 -107 This discussion about prognosis for different types of lesions is not relevant to the paper's title.

Authors' response: As additional detail about the discussion of lesion types was requested, this section was altered as suggested by reviewer 1. The authors would like to defer to the editor to decide how much information should be included here (lines 123-132).

Reviewer comment: Lines 110 - 121 Please be careful to make it absolutely clear whether you are describing the evolution of naturally occurring lesions versus experimentally -induced lesions - they are not the same!

Authors' response: Information regarding the type of lesion was included (lines 143-145).

Reviewer comment: Line 123 Now you say that 1 tesla is high-field!

Authors' response: The authors agree and the introduction of the MRI section was changed to be more precise (line 72).

Reviewer comment: Lines 161-4 reference required

Authors' response: The reference was added (line 198).

Reviewer comment: I think that you need to put into perspective the cost benefit ratio and time benefit ratio of the variety of injection techniques described and think about what is practical and what is in reality being done in practice. Many of these techniques were described > 10 years ago but have not been universally embraced.
Moreover the safety aspects and hassle factor (taking limbs in and out of a magnet) must also be considered.

Authors' response: The authors agree and the practical implications of the injection techniques, particularly when considered to be used during low-field MRI were added (also requested by reviewer 1) (lines 211-214).

Reviewer comment: Gadolinium - so do you conclude that with our current knowledge the extra costs and time involved are justified with respect to acquisition of knowledge that is going to influence patient management? I think that a review of this type has to be critical - rather than just describe what has been published - what is of practical value for patient management?

Authors' response: Similar to the previous paragraph, practical considerations were added to this section (lines 251-252). The value of contrast MRI is additionally critically appraised in lines 254-256; 256-259; 273-275.

Reviewer comment: Reviewer comment: Line 252- 264 In part 1 you described focussing on equine literature! Line 264 - is 9T imaging ever going to be affordable for equine practice? Fig. 2 provides some beautiful images but they don't really tell us how they might potentially give us additional useful clinical information over and above ultrasonography.
This seems to be another example of how this paper does not really relate enough to what can be usefully used clinically in the real world. Just because something can be done does not mean it should be done unless there is benefit to the clinician and patient.
The section on CT and contrast-enhanced CT is the best section of this paper.

Authors' response: The authors appreciate the reviewers concern and agree that some imaging techniques detailed throughout the review might not be practical or valuable enough to become widely accepted in the future. The aim of the review is to give the reader an idea of what research is focused on and what might be possible in the future.
The role of the interfascicular matrix in the pathogenesis of tendinopathy has been investigated in detail in recent years and is thought to have major implications in the development of clinically relevant tendon injury (Thorpe et al. 2012/2013). To the author's knowledge ultra-high field MRI is the only imaging technique that facilitates visualisation of the interfascicular matrix

to date. Whilst ultra-high field MRI is far from being introduced in equine practice, the field of diagnostic imaging is advancing rapidly in human as well as veterinary patients.

Thorpe, C.T., Udeze, C.P., Birch, H.L., Clegg, P.D., Screen, H.R.C., 2012. Specialization of tendon mechanical properties results from interfascicular differences. Journal of the Royal Society Interface 9, 3108-3117.

Thorpe, C.T., Udeze, C.P., Birch, H.L., Clegg, P.D., Screen, H.R.C., 2013. Capacity for sliding between tendon fascicles decreases with ageing in injury prone equine tendons: a possible mechanism for age-related tendinopathy? European Cells and Material 25, 48-60.

Reviewer comment: BUT, 'Further research should confirm the value of this technique for diagnostic purposes and pre-surgical planning' How will it help pre-surgical planning? - if you have effusion in the DFTS which you think is clinically significant and no detectable tendon or manica flexoria lesion determined using ultrasonography you are going to perform a comprehensive tenoscopic examination. If you have identified a lesion you are going to perform tenoscopy, unless the lesion has a poor prognosis.
Why involve the client in additional costs?

Authors' response: The authors agree that the befit of this technique is debatable, depending on the location of a lesion the contrast study may however indicate which recumbency is most appropriate for tenoscopy.

'The majority of equine surgeons perform tenoscopy with the horse in lateral recumbency, with the affected limb uppermost. If, for example, the horse was found at surgery to have a medial border deep digital flexor tendon tear, this would be difficult to debride with the limb uppermost. With computed tomographic contrast tenography and the ability to determine lesion laterality, the horse could be positioned appropriately to facilitate the best surgical access and hence improve outcome. Future study should be directed at investigating this technique for the evaluation of pathologic specimens.' (Agass et al., 2018, page 282).

Agass, R., Dixon, J., Fraser, B., 2017. Computed tomographic contrast tenography of the digital flexor tendon sheath of the equine limb. Veterinary Radiology & Ultrasound 59, 279-288.

Reviewer comment: Line 373 What evidence do you have for the very sweeping statement 'and has high potential for the prevention of tendon injury,'? If only it was that simple!

Authors' response: The sentence was adjusted with the phrase 'high potential' removed to ensure it sounds less sweeping (line 428).

Reviewer comment: Figure legends need to describe the orientation of the images. How do these images enhance the manuscript? It would be more useful to who examples of where a lesion could not be seen using conventional imaging but was seen with 'advanced imaging' or was not

seen on a non-contrast enhanced image but was seen on a contrast enhanced image - or at least you gained additional useful information from contrast enhancement.

Authors' response: The orientation of the images is now stated in the figure legends (lines 948; 954; 961, 968 and 987) and further images including contrast CT were added to the manuscript (Figure 1 + 4).