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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 --Manuscript Draft--

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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.

1	Review
2 3 4 5	Equine flexor tendon imaging part 2 – current status and future directions in advanced diagnostic imaging <u>, with focus on the deep digital flexor tendon</u>
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21 Abstract

22	Flexor tendon injuries are a common cause of lameness and early retirement in equine
23	athletes. Whilst ultrasonography is most frequently utilized, advanced diagnostic imaging
24	modalities are becoming more widely available for detection and monitoring of flexor tendon
25	lesions. Part two of this literature review aims to detail the current experience with low- and
26	high-field magnetic resonance imaging (MRI) and computed tomography (CT) for the
27	diagnosis of equine flexor tendinopathy. <u>Implications of the Recently described approaches</u>
28	including 'magic angle' artefactMRI as well as injection techniques and the use of contrast
29	are discussed. Besides lesion detection, future developments in tendon imaging focus on
30	gaining enhanced structural-and functional information about the tendon architecture with the
31	prospect to prevent injury. Techniques as described-in for the assessment of the human
32	Achilles tendon including ultra-high field MRI and positron emission tomography are
33	highlighted.
34	
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37 Introduction

38 Superficial digital Equine flexor tendon (SDFT) injury is most commonly seen in 39 racing Thoroughbreds whereas injuries of the deep digital flexor tendon (DDFT) affect 40 horses performing in a wide variety of disciplines (Takahashi et al., 2004; Lam et al., 2007; 41 Smith et al., 2007; Arensburg et al., 2011). The majority of DDFT lesions involve the distal 42 aspect of the tendon and are associated with concurrent pathology of the 43 podotrochlearnavicular apparatus and palmar foot pain in approximately 51-79% of cases 44 (Blunden et al., 2006; Blunden et al., 2009; Vanel et al., 2012; Cillan-Garcia et al., 2013). 45 Clinical examination and ultrasonography are often sufficient for the diagnosis of SDFT 46 injury. The increasing availability of advanced diagnostic imaging modalities for the 47 assessment of the equine digit has however greatly improved the diagnosis of DDFT 48 pathology over the past two decades, particularly as the hoof capsule limits the utility of 49 ultrasonography in this area (Tucker and Sande, 2001; Mair and Kinns, 2005; Dyson and 50 Murray, 2007; Sherlock et al., 2015; Jones et al., 2019). For the second part of this review the 51 current literature was systematically assessed as described in review part 1 in order to provide 52 an overview of recent developments and future prospects for equine flexor tendon advanced 53 diagnostic imaging. The following search terms were used in PubMed, Medline and Google 54 Scholar without restrictions: 'tendon' AND 'magnetic resonance imaging' OR 'computed tomography' AND 'equine' OR 'horse'. Additional studies were identified by searching the 55 56 reference list of eligible articles. 57

58 Low-field Magnetic resonance imagingRI

59 MRI for the evaluation of soft tissue injuries in equine patients was first introduced in 60 the early 1990s and has since become <u>widely used the gold standard</u> for tendon and ligament 61 imaging especially in the equine digit (Park et al., 1987; O'Callaghan, 1991; Denoix, 1994;

	62	Kotani et al., 2000; King et al., 2013; Bubeck and Aarsvold, 2018). An increasing number of	
	63	low-field (0.25 <u>to-<1</u> +Tesla) open MRI units are installed in equine referral practices across	
ļ	64	Europe, the US and other countries, and several studies have proven a good correlation	
	65	between <u>low- and high-field MR</u> imaging findings and histopathological diagnosis of tendon	
	66	disease (Kasashima et al., 2002; Murray et al., 2004; Blunden et al., 2006; Murray et al.,	
	67	2006; Blunden et al., 2009; Murray et al., 2009; Karlin et al., 2011; Sherlock et al., 2015)	
	68	(Table 1). Additionally, tendon injuries caused by foot penetrations or distal limb wounds can	
ļ	69	be diagnosed with high accuracy using standing low-field MRI (del Junco et al., 2012;	
	70	Meehan, 2017; Schiavo et al., 2018; Sherlock et al., 2019).	
	71		
	72	Low-field MRI	
ļ	73	MR image acquisition: the 'magic angle'	
	74	The 'magic angle' effect can impact on the interpretation of MR images depending on	
	75	the positioning of the limb in the magnetic field. The artefact is the result of characterized by	
	76	increased T2 relaxation timesignal that occurs when collagen fibres (which through strong	
ļ	77	dipolar interaction typically have very low MR signal) are oriented at approximately 55° to	
	78	the main magnetic field (B_0) during image acquisition (Erickson et al., 1991; Erickson et al.,	
	79	1993; Bydder et al., 2007; Murray et al., 2009). The 'magic angle' effect typically manifests	
	80	as focally increased signal and is usually found on short echo time sequences including T1-	
	81	weighted fast spin echo and proton density-weighted sequences-but may also be observed on	
	82	other sequences (Peh and Chan, 1998; Li and Mirowitz, 2003; Richardson et al., 2018). The	
	83	common sites and appearance of the artefact are well documented for the DDFT and	
	84	ligaments including the collateral ligaments of the distal interphalangeal joint (Spriet et al.,	
I	85	2007; Smith et al., 2008; Spriet and McKnight, 2009; Spriet and Zwingenberger, 2009;	
	86	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).

92

93 MRI for monitoring of tendon lesions

94 Since MRI has been established as a sensitive tool for the diagnosis of tendinopathies 95 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 96 97 resolution of STIR-FSE and T2-FSE signal changes over time appear to be positive 98 prognostic indicators, whilst most lesions remain visible on T1-GRE and PD images even in 99 cases with excellent outcome (Holowinski et al., 2010; Vanel et al., 2012). Horses with T1-100 GRE hyperintense DDFT lesions over 30mm in length or over 10% cross-sectional area, as 101 well as horses with persistent STIR-FSE signal or with concurrent lesions in the foot, are less 102 likely to return to their previous level of exercise (Dyson et al., 2005; Dyson and Murray, 103 2007; Vanel et al., 2012).

104

105The evolution developmentof different DDFT lesion types varies when assessed over106time. Dorsal border lesions showed a more rapid reduction in T2*-GRE volume and107ratiometric intensity (ratio between lesion and adjacent cortical bone) than parasagittal and108core lesions in clinical cases that were followed over a 6-month period (Milner et al., 2012).109No correlation between lameness and lesion signal intensity was found in this study, but110long-term telephone follow-up (18 months) of a larger group of horses confirmed that dorsal111border lesions seem to have a favourable prognosis for return to some level of activityridden

112	exercise (73%) when compared to other lesion types (core lesions 41%; parasagittal splits
113	50%) (Cillan-Garcia et al., 2013). However, overall only approximately 25% of these horses
114	returned to their previous level of exercise. Theis study additionally showed an effect of
115	lesion location with a worse prognosis identified for insertional or suprasesamoidean lesions
116	of the DDFT when compared to lesions at the level of the navicular bone. Lthat lesions
117	affecting both lobes of the DDFT wereare not necessarily associated with a worse prognosis
118	than uniaxial defects (Cillan-Garcia et al., 2013).
119	
120	Ultrasonography currently remains the most practical imaging modality for the
121	diagnosis and monitoring of SDFT lesions in a clinical setting (Bubeck and Aarsvold, 2018).
122	It is however important to note that the area of maximal cross-sectional injury in
123	experimentally induced SDFT lesions older than 4 weeks appears approximately 18% smaller
124	on ultrasonographic images when compared to standing low-field MRI (Schramme et al.,
125	2010; Karlin et al., 2011). Similar results were found in <u>naturally occurring SDFT</u>
126	lesionsother studies and should be taken into consideration when adjusting the exercise
127	program of a horse with SDFT tendinopathy based on ultrasonographic assessment alone
128	(Schramme et al., 2010; Berner et al., 2016). During sequential MRI examination, SDFT
129	lesions follow a pattern of signal change that differs from the pattern observed in DDFT
130	lesions over time. MR signal decreases earlier in T2-weighted images than in STIR-FSE
131	images in the SDFT (Schramme et al., 2010; Karlin et al., 2011; Berner et al., 2016; Berner,
132	2017; Berner et al., 2020).
133	

134 High-field MRI

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

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

145 'Magic angle MRI'

146 Similar to the appearance on low-field MRI where the B₀ magnetic field is oriented 147 vertically, the 'magic angle' effect at the distal aspect of the DDFT can be recognised mainly 148 on T1-weighted high-field MR images, when the long axis of the tendon is oriented at 149 approximately 55° (+/- 5-7°) to the horizontally oriented static magnetic field (Busoni and 150 Snaps, 2002; Spriet and McKnight, 2009; Werpy et al., 2010). The artefact is characterised 151 by a hyperintense signal and can impact on the interpretation of MR images (Erickson et al., 152 1991; Erickson et al., 1993). Since tendons generally present with little to no signal on MR 153 images, the intentional application of the 'magic angle' effect has been proposed to further 154 investigate the available signal of the tendon structure. The so called 'magic angle MRI' 155 allows sufficient signal to be obtained using the standard pulse sequences of clinical MRI 156 systems (Bydder et al., 2007). Using this technique, an increased T1 relaxation time has been 157 reported in cases of chronic Achilles tendinopathy in humans (Marshall et al., 2002; Oatridge 158 et al., 2003).

- 159
- 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

162	determined (Spriet et al., 2011). To further assess possible changes in T1 relaxation
163	associated with tendinopathy, both laser-induced and as well as naturally occurring SDFT
164	lesions were subsequently evaluated (Spriet et al., 2012). All naturally occurring lesions were
165	visible on conventional as well as on 'magic angle' MR images. Based on the histological
166	findings the authors state however, that 'magic angle MRI' might be advantageous for the
167	identification of diffuse changes in tendon composition, that appeared hypointense on
168	conventional MR imaging (Spriet et al., 2012). Whilst the feasibility of 'magic angle MRI'
169	has been demonstrated in high-and low-field MRI systems, the adequate positioning of the
170	limb may still prove to be a challenge in an <i>in vivo</i> setting (Spriet et al., 2012; Horstmeier et
171	al., 2019).
172	
173	Influence of local injection on MRI interpretation
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186 field_MR image interpretation (Daniel et al., 2019). The study showed that the presence of

18/	fluid significantly improved the delineation of the DDFT in both imaging modalities and the
188	visualisation of the margins of the SDFT on MR images. As the technique did not introduce
189	any artefacts or altered the dimensions of the intra-thecal structures, further evaluation in
190	clinical cases should be of value particularly for the detection of marginal tendon lesions. It is
191	however important to consider that patients might be reluctant to stand during low-field MRI
192	following distention of the digital flexor tendon sheath. Consequently, the technique appears
193	to be more suited for high-field MR evaluation.
194	
195	In order to facilitate assessment of the dorsal border of the DDFT at the level of the
196	navicular bone, the injection of the navicular bursa with saline (6-10 ml) or a mixture of
197	saline and contrast medium (5-6 ml, 1:1 ratio of 0.9% saline: Diatrizoate Meglumine and
198	Diatrizoate Sodium; Hypaque-76®) has been proposed (Schramme et al., 2009; Maher et al.,
199	2011). The distension of the navicular bursa physically separates the palmar surface of the
200	navicular bone from the dorsal margin of the DDFT and allows adhesions, DDFT fibrillation
201	and tendon splits at this level to be recognized more readily. The limitations of the technique
202	include the time required for the navicular bursa injection under radiographic guidance, and
203	the risk of rupture of the navicular bursa, especially if a volume in excess of 5 ml is injected
204	(Schramme et al., 2009; Maher et al., 2011). Alternatively, the distension of the distal
205	interphalangeal joint with saline (20-35 ml) alters the position of the proximal recess of the

206 navicular bursa and enhances the visualisation of the dorsal border of the DDFT, similar to

207 the direct approach to the navicular bursa (McGill et al., 2015). Both techniques are described

208 to be more reliable in the non-weightbearing limb when no pressure is exerted between the

209 navicular bone and the DDFT and are therefore probably more suitable for high-field MRI *in*

210 vivo (Maher et al., 2011; McGill et al., 2015).

212 Contrast-enhanced MRI

213	Gadolinium-based contrast-enhanced MRI is routinely performed forim human and
214	small animal neurologic, oncologic and vascular imaging (Owen, 2018; Scott, 2018).
215	Gadolinium shortens the relaxation time constants (T1 and T2) of the tissues, which leads to
216	an increase in signal intensity _a especially in T1-weighted images (Lin and Brown, 2007).
217	First clinical reports recommended an intra-venous gadopentate dimeglumine dose of 0.1
218	ml/kg (50 ml/horse) for musculoskeletal contrast-enhanced MRI in horses (Judy et al., 2008;
219	Saveraid and Judy, 2012; Daniel et al., 2013). The authors described the potential for an
220	improved recognition and assessment of tendon lesions, similar to the human Achilles
221	tendon, where a correlation between contrast enhancement and the severity of tendon lesions
222	has been demonstrated in a number of clinical cases (Shalabi et al., 2002; Richards et al.,
223	2010).
224	
225	In order to decrease the volume and associated expense of gadolinium required for
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225 226 227	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
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236	post tourniquet application. Additionally, it might be challenging to replicate the exact
237	position of the foot in the magnet pre- and post contrast injection.
238	
239	A further study compared systemic intra-venous injection with regional intra-arterial
240	injection of gadolinium in a group of horses with lameness localized to the foot (De Zani et
241	al., 2018). The injection of 0.02 ml/kg of gadolinium in the radial artery resulted in a higher
242	ratio of MRI contrast enhancement when compared to the systemic intra-venous route (0.1
243	ml/kg). Whilst the tendon tissue appeared generally not highly vascularised, significant
244	enhancement of the DDFT and peritendinous tissue was noted in the area of suspected
245	pathological lesions (De Zani et al., 2018).
246	
247	The contrast enhancement in association with tendinopathy is most likely related to an
248	increased capillary permeability and diffusion of blood into the interstitial space in the acute
249	stages of the injury. Additionally, neovascularisation and granulation tissue formation are
250	suspected to show increased contrast uptake. However, histological studies of contrast-
251	enhancing lesion in the equine distal limb are currently lacking (Shalabi et al., 2002; Saveraid
252	and Judy, 2012; Nelson et al., 2017).
253	
254	Side effects of the administration of gadolinium-based contrast agents are described in
255	human and small animal patients, but no severe adverse reactions were encountered in the
256	aforementioned equine studies (Wible et al., 2001; Grobner and Prischl, 2007; Lin and
257	Brown, 2007; Girard and Leece, 2010; Saveraid and Judy, 2012; Prince et al., 2017; Aarsvold
258	et al., 2018; De Zani et al., 2018). A recent review of the use of contrast media in horses
259	classified the risk associated with the administration of gadolinium generally as low,
260	provided horses do not suffer underlying renal disease or dehydration (Nelson et al. 2017)

1/).

261	Future research should further ascertain the benefits of contrast-enhanced over standard MRI
262	for the assessment of tendon lesions and identify how imaging findings correlate with
263	histopathology. Additionally, the combined approach of contrast-enhanced and 'magic angle
264	MRI' as described for the human Achilles tendon might be of interest for equine flexor
265	tendon imaging (Marshall et al., 2002).
266	
267	Ultra-high field MRI
268	The high-field MRI systems currently installed in veterinary centres for clinical
269	applications operate at a field strength of 1.5 to 3 T. Magnets used in humans for clinical
270	purposes have now reached 7 T, and preclinical research ultra-high field MRI systems
271	exceeding a field strength of 10 T are available (Alizai et al., 2018; Ladd et al., 2018).
272	
273	Low- and high-field MRI facilitates the detection and assessment of tendon lesions,
274	but the visualisation of the tendon structure remains difficult. The very short transverse
275	relaxation time of normal tendon tissue, with the relatively long echo times used in
276	conventional clinical MRI sequences usually result in the complete decay of tendon signal
277	before it can be sampled (Juras et al., 2012; Guidetti et al., 2018; Juras et al., 2019). With
278	increasing field strength and signal-to-noise ratio, and the use of ultrashort echo time (UTE)
279	and other sequences, MR images of the finer tendon structural components can be obtained
280	(Fig. 2) (Robson et al., 2004; Du et al., 2010; Moser et al., 2012; Juras et al., 2013; Chang et
281	al., 2015; Foure, 2016). In man, ultra-high field MRI is utilized to visualise the fascicular
282	pattern of the Achilles tendon in vivo (Han et al., 2014; Foure, 2016; Juras et al., 2019).
202	

284 Ultra-high field MRI of the equine SDFT

285	Ultra-high field MRI (9.4 T) of the equine SDFT facilitates the detailed assessment of
286	the tendon structure with clear delineation of the tendon fascicles and interfascicular matrix
287	(Fig. 2 A + B). Additionally, T2*-weighted 3D-FISP gradient echo transverse images provide
288	a comprehensive picture for the characterisation of tendon lesions (Fig. 2C). At this stage the
289	size of the radiofrequency coil and the time required to obtain this high level of anatomical
290	detail preclude the in vivo assessment of tendon lesions in horses. The cost and technical
291	expertise involved with MR imaging at higher field strength limits its availability in
292	veterinary medicine, however, ultra-high field MRI offers promising prospects for
293	musculoskeletal imaging as clinical progress continues (Alizai et al., 2018; Ladd et al., 2018).
294	
295	Computed tomography
296	The limited availability of MRI has led to the investigation of alternative modalities
297	for soft tissue advanced diagnostic imaging in equine orthopaedics (Tucker and Sande, 2001;
298	Puchalski, 2012; Jones et al., 2019). A study comparing MRI and CT for the assessment of
299	the equine distal limb found similar scores for the visibility of the DDFT in the area of the
300	pastern for both modalities, but the distal DDFT at the level of insertion showed better
301	visualisation scores with low-field MRI (Vallance et al., 2012a). Likewise, the classification
302	of DDFT lesions varies depending on the imaging modality used for interpretation. More
303	lesions of the distal DDFT were detected with low-field MRI but lesions at the level of the
304	pastern as well as abrasions and mineralisation of the DDFT were more likely to be
305	diagnosed with CT in a cohort of clinical cases (Fig. 3) (Vallance et al., 2012b). Additional
306	reports comparing both, MRI and CT imaging findings of the same subject with results of
307	histopathological examination would give further insight and support image interpretation
308	(Whitton et al., 1998; Puchalski et al., 2009).

310 Contrast-enhanced computed tomography

311	The contrast media used for CT studies in equine patients are usually iodinated
312	solutions that strongly attenuate X-rays and highlight areas of increased vascular perfusion or
313	permeability (Bushberg et al., 2012; Nelson et al., 2017). Following acquisition of pre-
314	contrast images tThe intra-vascular or intra-thecal route of administration may be chosen for
315	contrast-enhanced CT imaging of the equine distal limb (Puchalski, 2012; Nelson et al.,
316	2017).
317	
318	There are some reports of intra-venous contrast studies in the horse (Hunter et al.,
319	2016; Walker et al., 2017). However, the technique most commonly described is the regional
320	intra-arterial injection of contrast medium, including placement of a catheter in the medial
321	palmar artery at the level of the carpometacarpal joint under ultrasonographic guidance in the
322	anaesthetised horse. Steady-state infusion of a 1:1 dilution of ionic-iodinated contrast in
323	saline is subsequently maintained with a remotely controlled pressure injector (2 ml/s),
324	starting 3-5 seconds prior to CT examination (Collins et al., 2004; Puchalski et al., 2005;
325	Puchalski et al., 2007; Puchalski et al., 2009; Pollard and Puchalski, 2011b). Whilst tendon
326	lesions are less common in the hindlimb, contrast application via catheterisation of the lateral
327	dorsal metatarsal artery is also described (van Hamel et al., 2014) (Fig. 4). The normal CT
328	anatomy and attenuation values for tendon and ligament before and after intra-arterial
329	contrast administration have been documented in detail (Tietje et al., 2001; Puchalski et al.,
330	2007; Vallance et al., 2012a; Claerhoudt et al., 2014). The DDFT generally shows a slight but
331	significant increase in post-contrast attenuation (8-17 HU) that potentially impairs on the
332	clear anatomical visualisation of the tendon (Puchalski et al., 2007; Vallance et al., 2012a).

334	DDFT lesions in the area of the foot are usually characterised by marked contrast
335	enhancement (> 20 HU) that may be central, peripheral or diffuse (Puchalski et al., 2009;
336	Puchalski, 2011; Vallance et al., 2012b; van Hamel et al., 2014). Lack of contrast
337	enhancement has been occasionally observed in dorsal border lesions of the DDFT. A
338	sensitivity of 93% for lesion detection was determined following histopathological
339	examination of the affected tissue in one study (van Hamel et al., 2014). All false negative
340	results obtained in this study were at the level of the navicular bone where the visibility of the
341	DDFT is most limited on CT images (Vallance et al., 2012a; van Hamel et al., 2014). Clinical
342	studies have shown that lesions of the DDFT can also be diagnosed based on non-contrast-
343	enhanced CT (Tietje et al., 2001; Jones et al., 2019). However, lesions in the area of the
344	DDFT insertion were more likely to be identified post-contrast in one study (Vallance et al.,
345	2012b).
346	
347	CT contrast tenography may aid the evaluation of the flexor tendons as they course
348	through the digital flexor tendon sheath (Fig. 54). Consistent delineation of the flexor tendon
349	borders and the manica flexoria has been described after intra-thecal injection of nonionic-
350	iodinated contrast solution (60 ml) into the digital flexor tendon sheath of cadaver limbs

351 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-surgicalplanning.

354

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

359	assessment of clinical cases has considerably increased over the past decade (Puchalski,
360	2012; Riggs, 2018). High slice number multidetector CT scanners are becoming more widely
361	available and first examples of distal limb examination in standing horses have been reported
362	(Desbrosse et al., 2008; Koch et al., 2020; Mageed 2020; Pauwels et al., 2021). In contrast to
363	MR imaging WCT does not offer the capability of accurately detecting the fluid content
364	within a tendon lesion to date. However, with its improved image quality and fast acquisition
365	time, CT may provide a practical alternative to MRI for advanced diagnostic imaging of the
366	equine flexor tendons (Riggs, 2018; Jones et al., 2019). Future research should show whether
367	CT imaging is comparable to MRI regarding the assessment of lesion progression over time.
368	Additionally, patient tolerance regarding contrast procedures in the standing horse warrants
369	further investigation.
370	
371	Positron emission tomography
372	Positron Emission tomography (PET) is a nuclear medicine imaging technique mainly
373	used in the field of human oncology, but orthopaedic applications are also described in man
374	(Fischer et al., 2010; Fischer, 2013; Kim et al., 2015; Eliasson et al., 2016; Aide et al., 2019).
375	In contrast to gamma scintigraphy where planar images are obtained after the injection of a
376	radioactive agent, PET acquires cross-sectional images allowing for three-dimensional
377	assessment of the region of interest (Spriet, 2019). PET is usually combined with CT in order
378	to obtain functional and structural information. As this setup is currently difficult to realise in
379	large patients like horses, a PET scanner used for preclinical brain research has been adapted
380	for PET imaging of the equine distal limb. First reports of PET imaging in equine
381	orthopaedics mainly describe the benefits of the technique for the detection of osseous lesions
382	and enthesopathy (Spriet et al., 2016; Spriet et al., 2018; Spriet et al., 2019; Norvall et al.,
383	2020). PET imaging has been applied for the monitoring of the healing response after

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

Conclusion

391	The rapid and ongoing technological progress and particularly the influence of
392	modern computing has led to the development of a multitude of approaches for soft tissue
393	imaging. Not all techniques described in preclinical studies or human orthopaedic research
394	will be economical or practical enough to be carried through into veterinary clinical
395	diagnostics. However, the last two decades have shown how fast advanced diagnostic
396	imaging modalities including MRI and CT have been integrated in equine orthopaedics at
397	referral level. Both modalities have benefits and disadvantages, particularly for the
398	assessment of flexor tendon injuries. Detailed knowledge of MRI and CT approaches
399	including the implications of the 'magic angle' and the use of injection techniques and
400	contrast should aid image interpretation and selection of the appropriate modality. As
401	diagnostic imaging is crucial for the diagnosis and monitoring of equine tendinopathy and
402	potentially aids has high potential for the prevention of tendon injury, there is ongoing
403	demand for future studies in this developing field of research.
404	
405	Conflict of intertest statement
406	None of the authors has any financial or personal relationships that could
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920 <u>Table 1</u>

921 Overview of the literature validating magnetic resonance imaging (MRI) in the equine distal

922 <u>limb for the assessment of the superficial digital flexor tendon (SDFT) and the deep digital</u>

923 <u>flexor tendon (DDFT).</u>

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

925 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 <u>leftright</u>).
(A) Note the increased T2 signal intense 'magic angle' artefact at the mid- to lateral aspect of
the superficial digital flexor tendon (<u>SDFT</u>) (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 <u>(lateral is to the left)</u>. (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.

939

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 <u>(lateral is to the</u>
<u>left</u>). (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

950	enhancement associated with a core lesion of the DDFT in zone 4B (white arrow). (B)
951	Additionally, perilesional contrast attenuation was evident in both lobes of the DDFT in zone
952	P2A (white arrows) in the same horse.
953	
954	Fig. <u>54</u> . Computed tomographic (CT) images of the flexor tendons at the level of the digital
955	flexor tendon sheath with $(B + D)$ and without $(A + C)$ intra-thecal application of nonionic-
956	iodinated contrast. The superficial and deep digital flexor tendons can be recognized on
957	transverse (A) and sagittal (C) CT images using the soft tissue window. The outline of the
958	manica flexoria (white arrow) and the flexor tendons is highlighted following injection of the
959	digital flexor tendon sheath with contrast $(B + D)$ (lateral is to the left on Fig. 5 A and B)
l 960	(Images courtesy of Carolin Müller, Lucidity Diagnostics 2020).

1	Review
2	
3	Equine flexor tendon imaging part 2 – current status and future directions in advanced
4	diagnostic imaging, with focus on the deep digital flexor tendon
5	
6	
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20	

21 Abstract

22 Flexor tendon injuries are a common cause of lameness and early retirement in equine 23 athletes. Whilst ultrasonography is most frequently utilized, advanced diagnostic imaging 24 modalities are becoming more widely available for detection and monitoring of flexor tendon 25 lesions. Part two of this literature review aims to detail the current experience with low- and 26 high-field magnetic resonance imaging (MRI) and computed tomography (CT) for the 27 diagnosis of equine flexor tendinopathy. Implications of the 'magic angle' artefact as well as 28 injection techniques and the use of contrast are discussed. Besides lesion detection, future 29 developments in tendon imaging focus on gaining enhanced structural information about the 30 tendon architecture with the prospect to prevent injury. Techniques as described for the 31 assessment of the human Achilles tendon including ultra-high field MRI and positron 32 emission tomography are highlighted.

33

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

36 Introduction

37 Superficial digital flexor tendon (SDFT) injury is most commonly seen in racing 38 Thoroughbreds whereas injuries of the deep digital flexor tendon (DDFT) affect horses 39 performing in a wide variety of disciplines (Takahashi et al., 2004; Lam et al., 2007; Smith et 40 al., 2007; Arensburg et al., 2011). The majority of DDFT lesions involve the distal aspect of 41 the tendon and are associated with concurrent pathology of the podotrochlear apparatus in 42 approximately 51-79% of cases (Blunden et al., 2006; Blunden et al., 2009; Vanel et al., 43 2012; Cillan-Garcia et al., 2013). Clinical examination and ultrasonography are often 44 sufficient for the diagnosis of SDFT injury. The increasing availability of advanced 45 diagnostic imaging modalities for the assessment of the equine digit has however greatly 46 improved the diagnosis of DDFT pathology over the past two decades, particularly as the 47 hoof capsule limits the utility of ultrasonography in this area (Tucker and Sande, 2001; Mair 48 and Kinns, 2005; Dyson and Murray, 2007; Sherlock et al., 2015; Jones et al., 2019). For the 49 second part of this review the current literature was systematically assessed as described in 50 review part 1 in order to provide an overview of recent developments and future prospects for 51 equine flexor tendon advanced diagnostic imaging. The following search terms were used in PubMed, Medline and Google Scholar without restrictions: 'tendon' AND 'magnetic 52 53 resonance imaging' OR 'computed tomography' AND 'equine' OR 'horse'. Additional 54 studies were identified by searching the reference list of eligible articles.

55

56 Magnetic resonance imaging

57 MRI for the evaluation of soft tissue injuries in equine patients was first introduced in 58 the early 1990s and has since become widely used for tendon and ligament imaging 59 especially in the equine digit (Park et al., 1987; O'Callaghan, 1991; Denoix, 1994; Kotani et 60 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).

67

68 Low-field MRI

69 *MR* image acquisition: the 'magic angle'

70 The 'magic angle' effect can impact on the interpretation of MR images depending on 71 the positioning of the limb in the magnetic field. The artefact is the result of increased T2 72 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 73 74 field (B₀) 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 75 76 signal and is usually found on short echo time sequences including T1-weighted fast spin 77 echo and proton density-weighted sequences (Peh and Chan, 1998; Li and Mirowitz, 2003; 78 Richardson et al., 2018). The common sites and appearance of the artefact are well 79 documented for the DDFT (Spriet et al., 2007; Smith et al., 2008; Spriet and McKnight, 80 2009; Spriet and Zwingenberger, 2009; Gutierrez-Nibeyro et al., 2011). A recent report 81 emphasized the importance of the position of the long axis of the limb perpendicular to the 82 magnetic field also for low-field MRI of the SDFT. Leaning to one side as well as internal or 83 external limb rotation during MR image acquisition in the standing horse may create a 'magic 84 angle' artefact in the SDFT at the level of the pastern that should not be confused with tendon 85 pathology (Fig. 1) (Sherlock and Mair, 2016).
86

87 MRI for monitoring of tendon lesions

88 Since MRI has been established as a sensitive tool for the diagnosis of tendinopathies 89 in the equine patient, the value of repeated MRI for monitoring purposes has been further 90 investigated. Sequential MRI evaluation of DDFT lesions in clinical cases has shown that 91 resolution of STIR-FSE and T2-FSE signal changes over time appear to be positive 92 prognostic indicators, whilst most lesions remain visible on T1-GRE and PD images even in 93 cases with excellent outcome (Holowinski et al., 2010; Vanel et al., 2012). Horses with T1-94 GRE hyperintense DDFT lesions over 30mm in length or over 10% cross-sectional area, as 95 well as horses with persistent STIR-FSE signal or with concurrent lesions in the foot, are less 96 likely to return to their previous level of exercise (Vanel et al., 2012).

97

98 The evolution of different DDFT lesion types varies when assessed over time. Dorsal 99 border lesions showed a more rapid reduction in T2*-GRE volume and ratiometric intensity 100 (ratio between lesion and adjacent cortical bone) than parasagittal and core lesions in clinical 101 cases that were followed over a 6-month period (Milner et al., 2012). No correlation between 102 lameness and lesion signal intensity was found in this study, but long-term telephone follow-103 up (18 months) of a larger group of horses confirmed that dorsal border lesions seem to have 104 a favourable prognosis for return to some level of activity (73%) when compared to other 105 lesion types (core lesions 41%; parasagittal splits 50%) (Cillan-Garcia et al., 2013). However, 106 overall only approximately 25% of these horses returned to their previous level of exercise. 107 The study additionally showed an effect of lesion location with a worse prognosis identified 108 for insertional or suprasesamoidean lesions of the DDFT when compared to lesions at the 109 level of the navicular bone. Lesions affecting both lobes of the DDFT were not necessarily 110 associated with a worse prognosis than uniaxial defects (Cillan-Garcia et al., 2013).

111

112	Ultrasonography currently remains the most practical imaging modality for the		
113	diagnosis and monitoring of SDFT lesions in a clinical setting (Bubeck and Aarsvold, 2018).		
114	It is however important to note that the area of maximal cross-sectional injury in		
115	experimentally induced SDFT lesions older than 4 weeks appears approximately 18% smaller		
116	on ultrasonographic images when compared to standing low-field MRI (Schramme et al.,		
117	2010; Karlin et al., 2011). Similar results were found in naturally occurring SDFT lesions and		
118	should be taken into consideration when adjusting the exercise program of a horse with		
119	SDFT tendinopathy based on ultrasonographic assessment alone (Berner et al., 2016). During		
120	sequential MRI examination, SDFT lesions follow a pattern of signal change that differs from		
121	the pattern observed in DDFT lesions over time. MR signal decreases earlier in T2-weighted		
122	images than in STIR-FSE images in the SDFT (Schramme et al., 2010; Karlin et al., 2011;		
123	Berner et al., 2016; Berner, 2017; Berner et al., 2020).		
124			
125	High-field MRI		
126	Most high-field MRI systems with a field strength of 1 Tesla (T) and above are		
127	installed in larger referral centres. Examination is usually performed in a closed-bore magnet		
128	and requires the horse to be anaesthetised (Lutter et al., 2015). Due to the higher signal-to-		
129	noise ratio and corresponding increased image contrast and resolution, the tendon margins are		
130	better defined, and subtle lesions appear more conspicuous on high-field MR images when		

131 compared to standing low-field MRI (Ghazinoor et al., 2007; Murray et al., 2009). Whilst

focal lesions (≤ 1 mm in diameter) and subtle dorsal fibrillation of the DDFT may be visible

tendon lesions and adhesions are generally detected on low- and high-field MR images, small

134 on high-field MRI only (Murray et al., 2009).

135

136 'Magic angle MRI'

137 Similar to the appearance on low-field MRI where the B_0 magnetic field is oriented 138 vertically, the 'magic angle' effect at the distal aspect of the DDFT can be recognised mainly 139 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 140 141 Snaps, 2002; Spriet and McKnight, 2009; Werpy et al., 2010). The artefact is characterised 142 by a hyperintense signal and can impact on the interpretation of MR images (Erickson et al., 143 1991; Erickson et al., 1993). Since tendons generally present with little to no signal on MR 144 images, the intentional application of the 'magic angle' effect has been proposed to further 145 investigate the available signal of the tendon structure. The so called 'magic angle MRI' 146 allows sufficient signal to be obtained using the standard pulse sequences of clinical MRI 147 systems (Bydder et al., 2007). Using this technique, an increased T1 relaxation time has been 148 reported in cases of chronic Achilles tendinopathy in humans (Marshall et al., 2002; Oatridge 149 et al., 2003).

150

151 In an initial 'magic angle MRI' study on equine specimens, reference values for the 152 normal T1 relaxation times of the equine SDFT, DDFT and suspensory ligament were 153 determined (Spriet et al., 2011). To further assess possible changes in T1 relaxation 154 associated with tendinopathy, both laser-induced and naturally occurring SDFT lesions were 155 subsequently evaluated (Spriet et al., 2012). All naturally occurring lesions were visible on 156 conventional as well as on 'magic angle' MR images. Based on the histological findings the 157 authors state however, that 'magic angle MRI' might be advantageous for the identification 158 of diffuse changes in tendon composition, that appeared hypointense on conventional MR 159 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).

163 Influence of local injection on MRI interpretation

164 Research assessing the influence of diagnostic analgesia on MR image interpretation 165 showed that perineural analgesia of the palmar digital nerves, as well as intra-synovial 166 analgesia of the navicular bursa and the distal interphalangeal joint, do not significantly alter 167 MR images of the distal limb at 1.5 T (Black et al., 2013). Only the injection of 15 ml 168 mepivacaine into the digital flexor tendon sheath caused an iatrogenic increase in synovial 169 fluid volume as detected on MRI at 24 and 72 hours post injection (Black et al., 2013). The 170 study additionally described that needle tracts could not be appreciated consistently at any 171 injection site apart from the site of the navicular bursa injection, where some evidence for a 172 needle tract was detected in 10/15 limbs at 72 hours post injection.

173

174 Another study further investigated the influence of saline injection (30-35 ml) into the 175 digital flexor tendon sheath for the purpose of enhanced ultrasonographic and 1.5 T high-176 field MR image interpretation (Daniel et al., 2019). The study showed that the presence of 177 fluid significantly improved the delineation of the DDFT in both imaging modalities and the 178 visualisation of the margins of the SDFT on MR images. As the technique did not introduce 179 any artefacts or altered the dimensions of the intra-thecal structures, further evaluation in 180 clinical cases should be of value particularly for the detection of marginal tendon lesions. It is 181 however important to consider that patients might be reluctant to stand during low-field MRI 182 following distention of the digital flexor tendon sheath. Consequently, the technique appears 183 to be more suited for high-field MR evaluation.

185 In order to facilitate assessment of the dorsal border of the DDFT at the level of the 186 navicular bone, the injection of the navicular bursa with saline (6-10 ml) or a mixture of 187 saline and contrast medium (5-6 ml, 1:1 ratio of 0.9% saline: Diatrizoate Meglumine and 188 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 189 190 navicular bone from the dorsal margin of the DDFT and allows adhesions, DDFT fibrillation 191 and tendon splits at this level to be recognized more readily. The limitations of the technique 192 include the time required for the navicular bursa injection under radiographic guidance, and 193 the risk of rupture of the navicular bursa, especially if a volume in excess of 5 ml is injected 194 (Schramme et al., 2009; Maher et al., 2011). Alternatively, the distension of the distal 195 interphalangeal joint with saline (20-35 ml) alters the position of the proximal recess of the 196 navicular bursa and enhances the visualisation of the dorsal border of the DDFT, similar to 197 the direct approach to the navicular bursa (McGill et al., 2015). Both techniques are described 198 to be more reliable in the non-weightbearing limb when no pressure is exerted between the 199 navicular bone and the DDFT and are therefore probably more suitable for high-field MRI in 200 vivo (Maher et al., 2011; McGill et al., 2015).

201

202 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

210 improved recognition and assessment of tendon lesions, similar to the human Achilles

211 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.,

213 2010).

214

215 In order to decrease the volume and associated expense of gadolinium required for 216 contrast-enhanced MRI in horses, regional limb perfusion with gadopentate dimeglumine (5 217 ml in 5 ml 0.9% saline) via the palmar/plantar digital vein at the level of the mid 218 metacarpus/metatarsus was evaluated in a prospective clinical study (Aarsvold et al., 2018). 219 Pre- and post-contrast high-field (1.5 T) MRI was performed in anaesthetized horses in 220 lateral recumbency. Contrast enhancement in the distal limb was adequate provided the 221 tourniquet was secured in place. Multiple lesions were identified and were mostly visible on 222 pre-contrast as well as contrast-enhanced MR images. The authors describe, however, that the 223 technique aids the characterisation of lesions including adhesions and neovascularisation of 224 the DDFT (Aarsvold et al., 2018). In the standing horse the approach may be limited due to 225 difficulties in ensuring patients stand still for the requisite amount of time for the examination 226 post tourniquet application. Additionally, it might be challenging to replicate the exact 227 position of the foot in the magnet pre- and post contrast injection.

228

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 suspectedpathological lesions (De Zani et al., 2018).

236

237 The contrast enhancement in association with tendinopathy is most likely related to an 238 increased capillary permeability and diffusion of blood into the interstitial space in the acute 239 stages of the injury. Additionally, neovascularisation and granulation tissue formation are 240 suspected to show increased contrast uptake. However, histological studies of contrast-241 enhancing lesion in the equine distal limb are currently lacking (Shalabi et al., 2002; Saveraid 242 and Judy, 2012; Nelson et al., 2017). 243 244 Side effects of the administration of gadolinium-based contrast agents are described in 245 human and small animal patients, but no severe adverse reactions were encountered in the 246 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 247 248 et al., 2018; De Zani et al., 2018). A recent review of the use of contrast media in horses 249 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). 250 251 Future research should further ascertain the benefits of contrast-enhanced over standard MRI 252 for the assessment of tendon lesions and identify how imaging findings correlate with 253 histopathology. Additionally, the combined approach of contrast-enhanced and 'magic angle 254 MRI' as described for the human Achilles tendon might be of interest for equine flexor tendon imaging (Marshall et al., 2002). 255 256

257 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).

263 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 264 265 relaxation time of normal tendon tissue, with the relatively long echo times used in 266 conventional clinical MRI sequences usually result in the complete decay of tendon signal 267 before it can be sampled (Juras et al., 2012; Guidetti et al., 2018; Juras et al., 2019). With 268 increasing field strength and signal-to-noise ratio, and the use of ultrashort echo time (UTE) 269 and other sequences, MR images of the finer tendon structural components can be obtained 270 (Fig. 2) (Robson et al., 2004; Du et al., 2010; Moser et al., 2012; Juras et al., 2013; Chang et 271 al., 2015; Foure, 2016). In man, ultra-high field MRI is utilized to visualise the fascicular 272 pattern of the Achilles tendon in vivo (Han et al., 2014; Foure, 2016; Juras et al., 2019).

273

262

274 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

282	veterinary medicine, however, ultra-high field MRI offers promising prospects for
283	musculoskeletal imaging as clinical progress continues (Alizai et al., 2018; Ladd et al., 2018).
284	

285 **Computed tomography**

286 The limited availability of MRI has led to the investigation of alternative modalities 287 for soft tissue advanced diagnostic imaging in equine orthopaedics (Tucker and Sande, 2001; 288 Puchalski, 2012; Jones et al., 2019). A study comparing MRI and CT for the assessment of 289 the equine distal limb found similar scores for the visibility of the DDFT in the area of the 290 pastern for both modalities, but the distal DDFT at the level of insertion showed better 291 visualisation scores with low-field MRI (Vallance et al., 2012a). Likewise, the classification 292 of DDFT lesions varies depending on the imaging modality used for interpretation. More 293 lesions of the distal DDFT were detected with low-field MRI but lesions at the level of the 294 pastern as well as abrasions and mineralisation of the DDFT were more likely to be 295 diagnosed with CT in a cohort of clinical cases (Fig. 3) (Vallance et al., 2012b). Additional 296 reports comparing both, MRI and CT imaging findings of the same subject with results of 297 histopathological examination would give further insight and support image interpretation 298 (Whitton et al., 1998; Puchalski et al., 2009).

299

300 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 precontrast 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).

308	There are some reports of intra-venous contrast studies in the horse (Hunter et al.,
309	2016; Walker et al., 2017). However, the technique most commonly described is the regional
310	intra-arterial injection of contrast medium, including placement of a catheter in the medial
311	palmar artery at the level of the carpometacarpal joint under ultrasonographic guidance in the
312	anaesthetised horse. Steady-state infusion of a 1:1 dilution of ionic-iodinated contrast in
313	saline is subsequently maintained with a remotely controlled pressure injector (2 ml/s),
314	starting 3-5 seconds prior to CT examination (Collins et al., 2004; Puchalski et al., 2005;
315	Puchalski et al., 2007; Puchalski et al., 2009; Pollard and Puchalski, 2011b). Whilst tendon
316	lesions are less common in the hindlimb, contrast application via catheterisation of the lateral
317	dorsal metatarsal artery is also described (van Hamel et al., 2014) (Fig. 4). The normal CT
318	anatomy and attenuation values for tendon and ligament before and after intra-arterial
319	contrast administration have been documented in detail (Tietje et al., 2001; Puchalski et al.,
320	2007; Vallance et al., 2012a; Claerhoudt et al., 2014). The DDFT generally shows a slight but
321	significant increase in post-contrast attenuation (8-17 HU) that potentially impairs on the
322	clear anatomical visualisation of the tendon (Puchalski et al., 2007; Vallance et al., 2012a).
323	
324	DDFT lesions in the area of the foot are usually characterised by marked contrast
325	enhancement (> 20 HU) that may be central, peripheral or diffuse (Puchalski et al., 2009;
326	Puchalski, 2011; Vallance et al., 2012b; van Hamel et al., 2014). Lack of contrast
327	enhancement has been occasionally observed in dorsal border lesions of the DDFT. A
328	sensitivity of 93% for lesion detection was determined following histopathological
329	examination of the affected tissue in one study (van Hamel et al., 2014). All false negative
330	results obtained in this study were at the level of the navicular bone where the visibility of the
331	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-contrastenhanced 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).

336

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 nonioniciodinated 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.

344

345 Adverse reactions to the intravascular administration of iodinated contrast are rare in 346 horses but may include a transient increase in heart rate and blood pressure as well as local or 347 generalised skin reactions (Gunkel et al., 2004; Pollard and Puchalski, 2011a; Nelson et al., 348 2017). CT technology is advancing rapidly and the resolution of images obtained for the 349 assessment of clinical cases has considerably increased over the past decade (Puchalski, 350 2012; Riggs, 2018). High slice number multidetector CT scanners are becoming more widely 351 available and first examples of distal limb examination in standing horses have been reported 352 (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 353 354 a tendon lesion to date. However, with its improved image quality and fast acquisition time, 355 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 356

357 imaging is comparable to MRI regarding the assessment of lesion progression over time.

Additionally, patient tolerance regarding contrast procedures in the standing horse warrantsfurther investigation.

360

361 Positron emission tomography

362 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 363 364 (Fischer et al., 2010; Fischer, 2013; Kim et al., 2015; Eliasson et al., 2016; Aide et al., 2019). 365 In contrast to gamma scintigraphy where planar images are obtained after the injection of a 366 radioactive agent, PET acquires cross-sectional images allowing for three-dimensional 367 assessment of the region of interest (Spriet, 2019). PET is usually combined with CT in order 368 to obtain functional and structural information. As this setup is currently difficult to realise in 369 large patients like horses, a PET scanner used for preclinical brain research has been adapted 370 for PET imaging of the equine distal limb. First reports of PET imaging in equine 371 orthopaedics mainly describe the benefits of the technique for the detection of osseous lesions 372 and enthesopathy (Spriet et al., 2016; Spriet et al., 2018; Spriet et al., 2019; Norvall et al., 373 2020). PET imaging has been applied for the monitoring of the healing response after 374 Achilles tendon rupture in human patients and increased uptake of the glucose tracer ¹⁸F-375 fluorodeoxyglucose was detected in horses with SDFT and DDFT tendinopathy in one 376 exploratory study (Eliasson et al., 2016; Spriet et al., 2016). Future studies will further 377 determine the value of PET imaging for the assessment of the equine flexor tendons in 378 clinical cases (Spriet, 2019).

379

380 Conclusion

381 The rapid and ongoing technological progress and particularly the influence of 382 modern computing has led to the development of a multitude of approaches for soft tissue 383 imaging. Not all techniques described in preclinical studies or human orthopaedic research 384 will be economical or practical enough to be carried through into veterinary clinical 385 diagnostics. However, the last two decades have shown how fast advanced diagnostic 386 imaging modalities including MRI and CT have been integrated in equine orthopaedics at referral level. Both modalities have benefits and disadvantages, particularly for the 387 388 assessment of flexor tendon injuries. Detailed knowledge of MRI and CT approaches 389 including the implications of the 'magic angle' and the use of injection techniques and 390 contrast should aid image interpretation and selection of the appropriate modality. As 391 diagnostic imaging is crucial for the diagnosis and monitoring of equine tendinopathy and 392 potentially aids the prevention of tendon injury, there is ongoing demand for future studies in 393 this developing field of research. 394 395 **Conflict of intertest statement** 396 None of the authors has any financial or personal relationships that could 397 inappropriately influence or bias the content of the paper. 398 399 Acknowledgements 400 The authors gratefully acknowledge the assistance of Dr. Carolin Müller and Birte 401 Drees (Lucidity Diagnostics) with the preparation of the figures. 402 403 **References:** Aarsvold, S., Solano, M., Garcia-Lopez, J., 2018. Magnetic resonance imaging following 404 405 regional limb perfusion of gadolinium contrast medium in 26 horses. Equine Veterinary Journal 50, 649-657. 406 407

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910 **Table 1**

- 911 Overview of the literature validating magnetic resonance imaging (MRI) in the equine distal
- 912 limb for the assessment of the superficial digital flexor tendon (SDFT) and the deep digital
- 913 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

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.

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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).

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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

- 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).

















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

<u>Reviewer comment:</u> 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.

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

<u>Reviewer comment:</u> 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.

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

<u>Reviewer comment:</u> 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?

<u>Authors' response:</u> 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).

<u>Reviewer comment:</u> 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.

<u>Authors' response:</u> 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).

<u>Reviewer comment:</u> 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?

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

<u>Reviewer comment:</u> 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.

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

<u>Reviewer comment:</u> 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.

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

<u>Reviewer comment:</u> 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.

<u>Authors' response:</u> 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).

Reviewer #2:

<u>Reviewer comment:</u> 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.

<u>Authors' response:</u> 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:

<u>Reviewer comment:</u> 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.

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
<u>Authors' response:</u> 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).

<u>Reviewer comment:</u> '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?

<u>Authors' response:</u> 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).

<u>Reviewer comment:</u> 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).

<u>Reviewer comment:</u> 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.

<u>Authors' response:</u> 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).

<u>Reviewer comment:</u> 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).

<u>Reviewer comment:</u> 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).

<u>Reviewer comment:</u> The initial validation comparing histology and MRI was done using highfield MRI. Line 58 1 Tesla is not low-field!

<u>Authors' response:</u> 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.

<u>Reviewer comment:</u> 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).

<u>Reviewer comment:</u> 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.

<u>Authors' response:</u> 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.

<u>Reviewer comment:</u> 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.

<u>Authors' response:</u> 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).

<u>Reviewer comment:</u> 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!

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

<u>Reviewer comment:</u> 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).

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

<u>Authors' response:</u> 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).

<u>Reviewer comment:</u> 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).

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

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

<u>Reviewer comment:</u> Lines 161-4 reference required

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

<u>Reviewer comment:</u> 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.

<u>Authors' response</u>: 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).

<u>Reviewer comment:</u> 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?

<u>Authors' response:</u> 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.

<u>Reviewer comment:</u> 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.

<u>Authors' response:</u> 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.

<u>Reviewer comment:</u> 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?

<u>Authors' response:</u> 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.

<u>Reviewer comment:</u> 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!

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

<u>Reviewer comment:</u> 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.

<u>Authors' response</u>: 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).