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Use of concurrent scintigraphic and magnetic resonance imaging evaluation to improve understanding of the pathogenesis of injury of the podotrochlear apparatus

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Summary

Reasons for performing study: **Use of physiological methods of diagnostic imaging could provide insight into the pathogenesis of foot pain in live horses.**

Objectives: **To describe patterns and intensity of increased radiopharmaceutical uptake (IRU) in the navicular bone, and relate this to distribution and types of signal intensity change in the navicular bone and to the presence or absence of lesions of the related soft tissue structures detected using MRI.**

Materials and methods: **Scintigraphic and MR images of 264 horses with unilateral or bilateral foot pain were analysed and graded. A Spearman rank correlation was used to test for relationships between scintigraphic grade of the navicular bone and MRI scores for each region of the bone. Chi-square tests were used to test for associations between scintigraphy grade and presence of increased signal intensities, for differences in the proportion of focal and diffuse IRU between MRI grades, and for associations between an abnormal scintigraphic grade of the navicular bone and presence or absence of a lesion.**

Results: **There were significant positive correlations between scintigraphy grade and both maximum and total MRI grades for the navicular bone and between scintigraphy grade and the MRI grades for the flexor border, the distal border and medulla. However, there was no difference in the proportions of focal and diffuse IRU between navicular bone MRI grades, although diffuse IRU was relatively under-represented in *Grade 3* navicular bones. There was no association between IRU in the navicular bone and MR lesions of either the DSIL origin or the CSL insertion, however there was an association between IRU in the navicular bone and combined lesions of the CSL, DSIL and navicular bursa. In limbs with a DDFT lesion, navicular bone scintigraphic *Grades 2* and *3* were over-represented.**

Conclusions and clinical relevance: **Scintigraphy and MRI provide complementary information about the pathogenesis of lesions of the podotrochlear apparatus. Further understanding of these disease processes may eventually permit more targeted treatments.**

Introduction

Although foot pain has been historically attributed largely to osseous pathology, recent work has indicated the importance of soft tissue injury (Dyson *et al*. 2003a,b, 2004, 2005; Dyson and Murray 2004). Comparison between diagnostic imaging and pathology (Blunden *et al*. 2006a,b; Murray *et al*. 2006a) has led to improvements in understanding of the pathological changes within the foot, but these usually represent advanced stages of disease or injury. Use of physiological methods of diagnostic imaging, such as scintigraphy and magnetic resonance imaging (MRI), could potentially provide insight into the pathogenesis of foot pain in live horses.

Nuclear scintigraphy has been used to diagnose navicular disease (Trout *et al*. 1991; Keegan *et al*. 1996; Lauk and Wanschura 1998; Dyson 2002), but increased radiopharmaceutical uptake (IRU) in the navicular bone has not been well correlated with pathological abnormalities of the bone confirmed by *post mortem* examination. Increased radiopharmaceutical uptake (IRU) has also been identified in horses without foot-related lameness (Dyson 2002). Preliminary observations have been made relating IRU in the navicular bone with abnormalities of the bone detectable using magnetic resonance imaging (MRI) (Dyson *et al*. 2003a, 2005, 2006; Martinelli and Rantanen 2005).

MRI may reveal abnormalities of the navicular bone that are not detectable using radiography (Dyson *et al*. 2003a, 2005, 2006; Schneider *et al*. 2003, 2005; Mair *et al*. 2003; Martinelli and Rantanen 2005) and provide additional information in horses with radiological change (Whitton *et al*. 1998; Widmer *et al*. 2000; Murray *et al*. 2006b). The coexistence of injuries to the navicular bone and DDFT or other components of the podotrochlear apparatus (the collateral sesamoidean ligament [CSL], distal sesamoidean impar ligament [DSIL] and navicular bursa) (Dyson *et al*. 2003a,b, 2005, 2006; Mair *et al*. 2003; Schneider *et al*. 2003, 2005; Martinelli and Rantanen 2005) has been recognised clinically using MRI and verified by *post mortem* examination (Blunden *et al*. 2006a,b; Murray *et al*. 2006a). A number of different pathological processes appear to occur in the navicular bone detected using MRI (Dyson *et al*. 2006). However, RU in the navicular bone with the different types of MR findings has not

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been documented and could provide insight into adaptative and degenerative changes.

It was hypothesised that focal IRU in the navicular bone would be associated with a variety of abnormalities of the bone detected using MRI and that there would be associations between abnormal RU in the navicular bone and MR lesions of the CSL, DSIL and DDFT. The objectives of this study were to describe patterns and intensity of IRU in the navicular bone, and to relate this to distribution and types of signal intensity change in the navicular bone, and to the presence or absence of lesions of the related soft tissue structures detected using MRI.

Materials and methods

Case selection

All horses were examined at the Centre for Equine Studies of the Animal Health Trust between January 2001 and December 2004. Horses selected for inclusion in this study had unilateral or bilateral forelimb lameness that was abolished by perineural analgesia of the palmar (abaxial sesamoid) nerves. The horses had been selected for MR examination because the results of clinical, radiographic, nuclear scintigraphic and ultrasonographic examinations did not conclusively explain the degree of lameness. Both forelimbs were examined using scintigraphy and MRI irrespective of whether lameness was unilateral or bilateral. Horses were omitted from the study if the count in one of the lateral scintigraphic images was <150,000, or if the series of MR images was incomplete.

Acquisition and analysis of scintigraphic images

Lateral and dorsal pool phase scintigraphic images and lateral, dorsal and solar bone phase images of both front feet were acquired and analysed as previously described (Dyson 2002; Dyson and Murray 2007).

MR image acquisition

The pastern region and both front feet were examined by MRI using a human extremity radiofrequency coil, with the feet positioned in the isocentre of a short-bore, flared-end 1.5 Tesla GE Signa Echospeed magnet[1] (Dyson *et al*. 2003). Sagittal, dorsal and transverse MR images were obtained using 3-dimensional (3D) T1 weighted spoiled gradient echo (SPGR), 3D T2* gradient echo (GRE) and short inversion recovery (STIR) or fat saturated 3D T2* GRE sequences, with a slice thickness of 1.5 mm (SPGR and GRE images) or 4 mm (STIR).

Analysis of MR images

The MR images were subjectively evaluated prospectively by one of 2 trained analysts (R.M. or G.G.). The images were also examined retrospectively by S.D. in order to grade abnormalities of the navicular bone on a scale of 0–3 using a previously documented method (Murray *et al*. 2006a) (Table 1; Figs 1–7 see www.evj.co.uk/suppinfo). For the purposes of statistical analysis the presence or absence of lesions of the CSL, DSIL, navicular bursa and DDFT were recorded. The DDFT was defined with respect to location and lesion type and an overall grade was assigned, defined as the presence or absence of a lesion distal to

TABLE 1: (adapted from Murray *et al.* 2006b) Criteria used for MR grading

Structure	Grade	Description
NB Flexor	0	Clear fibrocartilage layer over entire surface, smooth chondro-osseous margins, uniform cortical thickness and smooth endosteal surface.
	1	Mild irregularities in the fibrocartilage thickness and signal intensity and/or slightly irregular chondro-osseous margin and/or slightly irregular endosteal surface.
	2	Moderate loss of signal definition at site of fibrocartilage with defects in the flexor surface of the cortex and/or moderate irregularity and loss of definition to the endosteal surface of the cortex.
	3	Severe fibrocartilage loss, large defects in the flexor surface of cortex, severe irregularities in the endosteal surface with extensions into medulla.
NB Distal	0	Smooth indentations into cortical surface, uniform cortical thickness, smooth endosteal surface.
	1	Slightly irregular indentations into cortical surface, mild variability in cortical thickness and/or slightly irregular endosteal surface.
	2	Irregular defects into the cortex with moderate variability in cortical thickness, endosteal irregularity and proximal linear extensions of mineralisation into the medulla.
	3	Severe, large defects in the cortex, surrounded by irregular mineralisation, distal border fragments, severe irregularity to the endosteal surface with marked extensions of mineralisation into medulla.
NB Dorsal	0	Clear articular cartilage layer over entire surface, smooth chondro-osseous margins, uniform subchondral bone thickness and smooth subchondral/cancellous junction.
	1	Mild irregularities in the articular cartilage thickness and signal intensity and/or slightly irregular chondro-osseous margin and/or slightly irregular subchondral/cancellous junction.
	2	Moderate loss of signal definition in articular cartilage with osteophyte formation and/or defects in the subchondral bone.
	3	Severe articular cartilage loss, osteophytes, large defects in the subchondral bone, severe irregularities in the subchondral/cancellous junction with extensions into medulla.
NB Proximal	0	Smooth indentation into cortical surface immediately dorsal to insertion of CSL, uniform cortical thickness, smooth endosteal surface.
	1	Slightly irregularity of cortical surface, mild variability in cortical thickness and/or slightly irregular endosteal surface.
	2	Moderate irregularity cortical surface, entheseophyte formation with moderate variability in cortical thickness, endosteal irregularity.
	3	Severe, marked cortical irregularity and entheseophyte formation, severe irregularity to the endosteal surface with marked extensions of mineralisation into medulla.
NB Medulla	0	Uniform high signal intensity on T1 and T2, with low signal intensity on fat-suppressed images. Clear definition from cortex.
	1	Less uniform high signal intensity on T1 and T2 with some signal heterogeneity. No alteration or mild focal, or very mild generalised increase in signal intensity on fat-suppressed images.
	2	Mild to moderate signal heterogeneity on T1 and T2 and/or moderate localised or generalised increase in signal intensity on fat-suppressed images.
	3	Marked alterations in signal intensity on T1 and T2 and/or generalised or focal marked alteration in signal intensity on fat-suppressed images.

0 = normal, 1 = mild abnormality, 2 = moderate and 3 = severe abnormality. DDFT - deep digital flexor tendon; NB - navicular bone; DSIL - distal sesamoidean impar ligament; CSL - collateral sesamoidean ligament.

the metacarpophalangeal joint. The location of the DDFT was defined as the level of the: insertion, DSIL, navicular bone, proximal aspect of the navicular bursa/CSL, proximal interphalangeal (PIP) joint and proximal phalanx. Each border of the navicular bone (palmar or flexor, distal, dorsal, proximal) and medulla were assessed separately, and overall grades for the navicular bone were also assigned: the maximum grade (the highest grade of any region) and the total grade (the sum of the grades for all regions). In addition the presence or absence of increased signal intensity in sagittal fat-suppressed images at the insertion of the CSL or the origin of the DSIL, or within a distal border synovial invagination were recorded. The presence or absence of fibrocartilage loss characterised by focal fluid accumulation palmar to the navicular bone in T2 weighted or fat-suppressed images was also documented.

Statistical analysis

A Spearman rank correlation was used to test for relationships between scintigraphic grade of the navicular bone and MRI scores for each region of the bone. Chi-square tests were used to test for: a) an association between scintigraphy grade and the presence of increased signal intensity at the insertion of the CSL, at the origin of the DSIL or in a synovial invagination, or the presence of a fibrocartilage defect; b) a difference in the proportion of focal and diffuse IRU between MRI grades for the total navicular bone and for each aspect of the navicular bone; and c) the association between an abnormal scintigraphic grade of the navicular bone and the presence or absence of a lesion of the DDFT, the CSL, the DSIL, the distal interphalangeal (DIP) joint or the navicular bursa. Data for left and right limbs were compared using a Mann Whitney U test. Statistical analysis was performed using statistical analysis software (Analyse-it)[2]. Level of significance was set at $P<0.05$.

Results

Two hundred and sixty-four horses were included in the study. The data for left and right front feet were analysed separately, but there was no significant difference between them, therefore only the results of the pooled data are reported.

Navicular bone

The frequency of scintigraphic abnormalities of the navicular bone is reported elsewhere (Dyson and Murray 2007). For the flexor aspect of the navicular bone the majority of horses had an MRI *Grade 0* (40.9%) or *Grade 1* (38.1%), with 17.7% having *Grade 2* abnormalities and 3.1% *Grade 3*. A similar distribution was seen for the medulla, with 39.0% and 34.7% *Grade 0* or *1* respectively, and 21.7% having *Grade 2* abnormalities and 4.6% *Grade 3*. A higher proportion of navicular bones were *Grade 0* or *1* for both the dorsal (68.0% and 25.8%) and proximal (50.0% and 34.1%) borders compared with the flexor border and medulla, but a larger proportion were *Grade 3* (dorsal 0.25%, proximal 21.95%). *Grades 1* (34.1%), *2* (22.7%) and *3* (28.35%) predominated for the distal border of the navicular bone.

There were significant positive correlation between the scintigraphy grade and: total MRI grade for the navicular bone ($P = 0.0005$); maximum MRI grade ($P = 0.0069$); flexor border MRI grade ($P = 0.0102$); distal border MRI grade ($P = 0.0006$); and medulla MRI grade ($P<0.0001$). However, there was no significant correlation between scintigraphy grade and MRI grade for either the proximal or dorsal borders.

There was no difference in the proportions of focal and diffuse IRU between navicular bone MRI grades (total or maximum). When the proportions of focal and diffuse IRU were compared for regions of the navicular bone, there was a trend towards a difference in proportion of diffuse and focal for the flexor border ($P = 0.06$), but for no other regions. For the flexor border, diffuse IRU was relatively over-represented in MRI *Grade 1* navicular bones and under-represented in MRI *Grade 3* navicular bones.

Focal increased signal intensity in fat-suppressed images at the insertion of the CSL was seen in 56.2% of limbs, at the origin of the DSIL in 48.3% and in a synovial invagination in 31.4%. Focal fluid accumulation on the palmar aspect of the navicular bone was seen in 31.4% of limbs. There was no relationship between scintigraphic grade for the navicular bone and any of these observations.

There was a significant association between IRU grade in the navicular bone and the presence of a lesion of either the navicular bursa ($P = 0.006$) or the CSL ($P = 0.0093$), but not for lesions of the DIP joint or the DSIL. However, there was an association between IRU grade in the navicular bone and the presence of combined lesions of the CSL, DSIL and navicular bursa ($P = 0.0132$).

Deep digital flexor tendon

For 436 limbs with DDFT lesions distal to the fetlock on MR images, 62% had scintigraphic *Grade 0* for the navicular bone, 29% *Grade 1*, 8% *Grade 2* and 2% *Grade 3*. For 75 limbs without DDFT lesions on MR images, 76% had scintigraphic *Grade 0* for the navicular bone, 20% *Grade 1*, 4% *Grade 2* and none *Grade 3*. When scintigraphic grade for the navicular bone was compared with the presence or absence of a DDFT lesion distal to the fetlock, there was a nonsignificant trend ($P = 0.09$) towards a difference in the proportion of scintigraphic grades between limbs with and without DDFT lesions. However, when navicular bone scintigraphic grades were compared with DDFT lesions at different levels, there was a significant difference in the proportions for lesions in the DDFT at the level of the navicular bone ($P = 0.008$), PIP joint ($P = 0.004$) and DSIL ($P = 0.05$), with a strong trend at the level of the CSL ($P = 0.059$), but no effect at the insertion. Scintigraphic *Grades 2* and *3* were relatively over-represented in the limbs with a DDFT lesion compared with those without.

Discussion

There were significant positive correlations between scintigraphy grade and both maximum and total MRI grades for the navicular bone and between scintigraphy grade and the MRI grades for the flexor border, distal border and medulla, supporting the hypothesis. However, contrary to the hypothesis there was no difference in the proportions of focal and diffuse IRU between navicular bone MRI grades, although diffuse IRU was relatively under-represented in MRI *Grade 3* navicular bones. Contrary to the hypothesis there was no association between IRU in the navicular bone and MR lesions of either the DSIL origin or the CSL insertion, however there was an association between IRU in the navicular bone and combined lesions of the CSL, DSIL and navicular bursa. In limbs with a DDFT lesion, navicular bone scintigraphic *Grades 2* and *3* were over-represented.

Increased RU predominantly reflects abnormal osteoblastic activity (Shani *et al*. 1990; Schwartz *et al*. 1993), however

altered bone modelling or remodelling could be adaptive or pathological. In this study, which comprised horses that were lame either unilaterally or bilaterally, there were no significant differences between data for left and right front feet. Although lameness may manifest unilaterally, in some horses abnormal modelling may occurring bilaterally, supporting similar clinical observations that pathological changes can be seen bilaterally in MR images in unilaterally lame horses (Dyson *et al*. 2005).

There was an over-representation of limbs with scintigraphic *Grades 2* and *3* for the navicular bone in limbs with a DDFT lesion at the level of the PIP joint, navicular bone or DSIL compared with those without. This suggests a direct relationship between lesions of the DDFT at these levels and lesions of the navicular bone and supports pathological observations in more advanced cases of disease (Blunden *et al*. 2006a). However, there did not appear to be an interaction between lesions of the DDFT at the level of either the proximal phalanx or the tendon's insertion and abnormal modelling of the navicular bone. These DDFT lesions may have a different aetiology and may not be part of the same disease process.

Scintigraphy was not sensitive for detection of pathology of the DSIL. However, when combined lesions of the CSL, DSIL and navicular bursa were considered there was a strong association with IRU in the navicular bone. There was also an association between IRU in the navicular bone and the presence of a lesion in either the CSL or the navicular bursa. Contact studies between the phalanges in isolated limbs have demonstrated that the greatest forces are applied to the podotrochlear apparatus in the propulsion phase of the stride, with increased pressure of the DDFT on the palmar aspect of the navicular bone, increased contact between the navicular bone and the middle phalanx and increased tension in the CSLs (Denoix 1999). Therefore the coexistence of lesions of the components of the podotrochlear apparatus is not surprising.

A diffuse increased signal intensity in fat-suppressed images in the spongiosa of the navicular bone resulted in an MRI *Grade 3*. Increased signal intensity in fat-suppressed images associated with reduced signal intensity in T1-weighted images may reflect a variety of pathological processes including fibrosis, necrosis, bone oedema or abnormal trabecular modelling (Bergman *et al*. 1994; Zanetti *et al*. 2000). Generalised trabecular necrosis and necrosis of interstitial fat of the spongiosa as the principle pathological abnormality of the navicular bone has been described previously (Blunden *et al*. 2006a). If bone necrosis predominated, mediated principally by osteoclasts, RU may be normal, resulting in a false negative scintigraphic result. In the current study, 22 limbs had an MRI *Grade 3* for the medulla, 11 of which had diffuse increased signal intensity in the navicular bone in fat-suppressed images and hypointense signal in T1-weighted images as the principle abnormality seen on MR images associated with a navicular bone scintigraphy score of 0 (n = 7) or 1 (n = 4).

MRI *Grade 3* abnormalities were potentially over-represented for the proximal, dorsal and distal borders of the navicular bones because of the presence of entheseophytes, dorsoproximal osteophytes and distal border fragments respectively. *Grade 2* abnormalities were more difficult to identify and may have been under-represented. MRI *Grade 3* abnormalities of the proximal and dorsal borders were not correlated with scintigraphy grade.

Dorsoproximal osteophytes may be a manifestation of DIP joint disease. Proximal entheseophytes can be an incidental radiographic finding in some sound horses if seen without other osseous abnormality, especially on the lateral aspect (Butler *et al*. 2000), presumably reflecting chronic stress at the insertion of the CSL. The majority of limbs had MRI *Grades 1–3* for the distal border of the navicular bone because of either mineralisation extending into the bone associated with distal border synovial invaginations, or the presence of fragments at the medial and/or lateral angle of the navicular bone. There was a significant correlation between the scintigraphy grade and the distal border MRI grade, indicating that these abnormalities on MR images are associated with altered bone modelling, either at these sites or elsewhere within the bone.

This study had some limitations. The prevalence of scintigraphic *Grade 3* lesions of the navicular bone was underestimated compared with our clinic population, because these are often associated with radiographic abnormalities that are diagnostic. Therefore, these horses would not have been subjected to MRI, although some of the radiographic lesions were actually quite subtle (e.g. flexor cortex defects seen only in high quality palmaroproximal-palmarodistal oblique views). Horses with 'end-stage' navicular disease were not examined; horses with advanced mineralisation of the navicular bone, evident radiographically, may have normal RU because bone modelling is no longer increased. The study did not relate lesions to the lame limb(s). There were no differences between data for the left and right limbs. We have observed clinically that, even in unilaterally lame horses, MRI signal intensity abnormalities are often seen bilaterally and speculate that this may reflect different stages of the disease process. It also highlights the lack of knowledge about what mediates pain.

Scintigraphy highlights the potential significance of some radiological abnormalities the significance of which may previously have been overlooked, e.g. increased thickness of the flexor cortex and subtle changes in corticomedullary demarcation. Such radiological abnormalities are generally associated with increased signal intensity in the palmar aspect of the spongiosa of the navicular bone in fat-suppressed MR images and endosteal and chondral irregularity of the flexor cortex of the navicular bone, often in association with other lesions of the podotrochlear apparatus.

Scintigraphy and MRI provide complementary information about the different disease processes affecting the podotrochlear apparatus. Although there were significant positive correlations between scintigraphic and MRI grades for the navicular bone, in some horses with diffuse hyperintense signal in the medulla in fat-suppressed images there was no marked IRU. If bone necrosis was the primary pathological process, it is possible that the use of a biphosphonate such as tiludronate may modify this disease process by inhibition of osteoclasis.

In conclusion, this study provides further evidence that a variety of pathological processes may involve the navicular bone, either alone or in association with concurrent lesions of the DSIL and CSL or the DDFT. Lesions of the DDFT at its insertion or at the level of the proximal phalanx may have a different aetiology to those at intermediate sites.

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[1]General Electric, Milwaukee, USA.
[2]Analyse-it Software Ltd., Leeds, UK.

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