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Review Article

A review of tendon injury: Why is the equine superficial digital flexor tendon most at risk?

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Summary

Tendon injury is one of the most common causes of wastage in the performance horse; the majority of tendon injuries occur to the superficial digital flexor tendon (SDFT) whereas few occur to the common digital extensor tendon. This review outlines the epidemiology and aetiology of equine tendon injury, reviews the different functions of the tendons in the equine forelimb and suggests possible reasons for the high rate of failure of the SDFT. An understanding of the mechanisms leading to matrix degeneration and subsequent tendon gross failure is the key to developing appropriate treatment and preventative measures.

Introduction

Tendon injury is one of the most common forms of musculoskeletal injuries that occur to horses competing in all disciplines, although tendon injuries in racehorses are the most investigated. Injuries to the musculoskeletal system have been found to account for 82% of all injuries to racehorses competing in National Hunt and flat races, and of these 46% involved tendons or ligaments (Williams *et al.* 2001; Ely *et al.* 2004). Another study reported that tendon or ligament strain accounts for 53% of musculoskeletal injuries that occur during hurdle and steeplechase races (Pinchbeck *et al.* 2004). A 12 year epidemiological study found that tendon injury was the most common reason for retirement in racing Thoroughbreds in Hong Kong (Lam *et al.* 2007). Furthermore, it has been found that, over the period of one season, 15% of both National Hunt horses (Ely *et al.* 2004) and Thoroughbred flat racehorses (Kasashima *et al.* 2004) in training suffered from a tendon or ligament injury as diagnosed by ultrasound. Some tendons are much more prone to injury than others; the majority of tendon injuries (97–99%) occur to the forelimb tendons (Kasashima *et al.* 2004; Lam *et al.* 2007), with the superficial digital flexor tendon (SDFT) being injured in 75–93% of cases and the remaining injuries occurring to the suspensory ligament (SL) (Ely *et al.* 2004; Kasashima *et al.* 2004). Prevalence of SDFT pathology has been found to be 24% in National Hunt horses in training that were assessed ultrasonographically over 2 seasons (Avella *et al.* 2009). Injuries to the mid-metacarpal tensional region of the deep digital flexor tendon (DDFT) and common digital extensor tendon (CDET) are rare, although injures to the DDFT at both the phalangeal level (Murray *et al.* 2006a) and within the digital sheath (Smith and Wright 2006) are reported; however, the prevalence of such injuries is not yet clear. The risk of tendon injury increases with increasing age (Ely *et al.* 2004, 2009; Kasashima *et al.* 2004; Perkins *et al.* 2005), and is more common in National Hunt horses than in those racing on the flat (Williams *et al.* 2001). There are several differences between National Hunt horses and flat racehorses that may account for the higher incidence of tendon injury in National Hunt racing.

National Hunt horses tend to be older than those that race on the flat, and compete over longer distances and for more seasons (Williams *et al.* 2001). Their tendons are also likely to be placed under higher strains when landing over fences. Some studies have reported a higher risk of tendon injury in entire male horses (Kasashima *et al.* 2004; Perkins *et al.* 2005; Lam *et al.* 2007) but other studies do not support this finding as they are unable to differentiate between entire males and geldings due to the small number of entire males studied (Ely *et al.* 2004, 2009). There is little information available regarding tendon injury in horses competing in other disciplines. However, it has been reported that tendon injury accounts for 43% of injuries that occur to event horses in training, with 33% of injuries to the SDFT, 31% to the SL and 17% to the DDFT (including injuries to the accessory ligament) (Singer *et al.* 2008). Elite show jumpers have been reported to have a high risk of injury to the forelimb SDFT and DDFT, whereas horses competing in dressage have a high risk of injury to the hindlimb SL based on cases referred to one referral centre with orthopaedic injury (Murray *et al.* 2006b).

Tendon injury is frequently preceded by degenerative changes in the extracellular matrix (Birch *et al.* 1998) rather than as the result of a single overloading event, but it is not clear what causes this initial degeneration. A similar degenerative change precedes injury in human tendons; and as in equine tendon often this is not

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accompanied by an inflammatory response and degenerative conditions that affect tendons are therefore now referred to as tendinopathies rather than tendinitis (Riley 2008). The tendon healing response is slow and inadequate; the defect is replaced by scar tissue which is likely to be weaker than the original tissue (Corr *et al.* 2009) and therefore there is a high risk of re-injury. It has been reported that 23–67% of horses with tendon injury treated using conservative methods will re-injure their tendons within 2 years of the original injury (Marr *et al.* 1993; Dyson 2004). It is important therefore to determine the causes of matrix degeneration to be able to develop effective preventative measures as well as treatment programmes for tendon injury.

Tendon function

Tendons in the equine forelimb act mainly to position the limb correctly during locomotion. Some tendons have an additional function, acting as springs to store and release energy as they are stretched and recoil during the stance and swing phase of each stride and so decrease the energetic cost of locomotion (Alexander 1991). The SDFT and SL are the main energy storing structures in the equine forelimb and are subjected to higher strains than the DDFT and CDET, which do not contribute significantly to energy storage (Wilson *et al.* 2001). During gallop, *in vivo* strains of 16% in the SDFT have been recorded (Stephens *et al.* 1989), which is similar to the failure strains of 15–17% recorded *in vitro* (Dowling *et al.* 2002; Gerard *et al.* 2005). In contrast, maximum *in vivo* strain for the CDET has been estimated at 2.5% (Birch *et al.* 2008a), which is almost 4 times lower than the failure strain of 9.7% recorded *in vitro* (Batson *et al.* 2003). Although the DDFT is situated on the palmar aspect of the limb between the SDFT and SL, its corresponding muscle exhibits differences in muscle architecture and fibre type compared to the SDF muscle, and its primary function appears to be flexion of the distal phalangeal joint during late swing rather than storage and return of energy (Butcher *et al.* 2009). Correspondingly, *in vivo* studies have shown than the DDFT experiences lower peak forces and strains during locomotion than the SDFT or SL (Platt *et al.* 1994; Butcher *et al.* 2007).

The function of a tendon is reflected in the mechanical properties of the tendon tissue. Although there is a large variation in SDFT strength and stiffness between individual horses (Birch

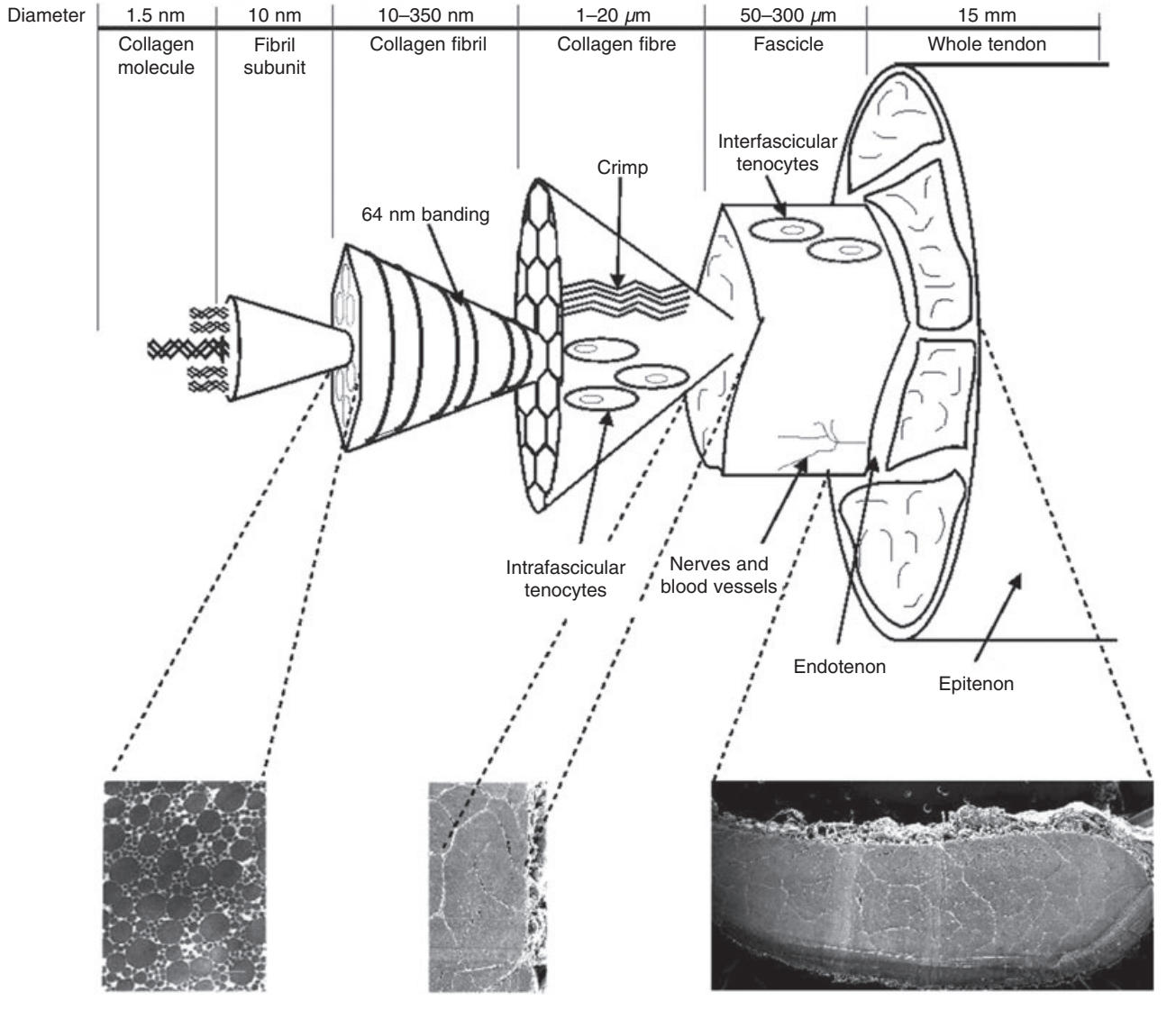

Fig 1: Representation of hierarchical structure of equine superficial digital flexor tendon.

2007); within an individual the SDFT invariably has a lower elastic modulus (less stiff material) than the CDET. The lower elastic modulus of the SDFT tissue means it can store and return energy more efficiently as it is stretched throughout the stance phase and recoils during the swing phase, returning the stored energy at an appropriate point in the stride cycle (Batson *et al.* 2003). Differences in mechanical properties arise from variation in the structure and molecular composition of the tendon matrix.

Tendon composition and structure

The specialised molecular composition and organisation of tendon results in a high strength structure able to resist unidirectional forces. Tendons consist of a dense fibrous extracellular matrix with a high water content, which is synthesised and maintained by a small population of tenocytes. The matrix is composed mainly of *type I* collagen, with a small percentage of other collagens and noncollagenous proteins. Collagen fibrils are orientated in the direction of force application and are arranged in a hierarchical structure (Kastelic *et al.* 1978), grouping together to form fibrils, fibres and fascicles, which make up the whole tendon (Fig 1). Collagen molecules are stabilised by intermolecular chemical crosslinks resulting in high tensile strength (Avery and Bailey 2005). Proteoglycans and glycoproteins are the most abundant noncollagenous proteins found in tendon but their functions have not been fully determined. Proteoglycans are thought to regulate fibrillogenesis and organise the matrix; the protein core binds to the collagen fibril at specific sites and the glycosaminoglycan (GAG) side-chains interact with side-chains from other proteoglycans, holding the fibrils at defined distances from each other (Scott 1995).

It has also been proposed that proteoglycans contribute to the mechanical properties of tendon directly, increasing the resistance to tensile loading by forming bridges between adjacent collagen fibrils and so assisting in the transfer of strain between the fibrils (Scott 2003; Screen *et al.* 2005). The most abundant glycoprotein found in tendon is collagen oligomeric matrix protein (COMP), the precise function of which is unknown, although it has been found that COMP is able to bind fibrillar collagen and so may be involved in fibrillogenesis and tendon growth (Smith *et al.* 2002). However, knockout studies have found that COMP-null mice do not exhibit any tendon abnormalities (Svensson *et al.* 2002). In healthy tendon the matrix is maintained and repaired by a small resident population of tenocytes which are situated between the collagen fibres within fascicles (intrafascicular) or reside between the collagen fascicles (interfascicular) (Fig 2). Tenocytes have long cytoplasmic processes which link to other tenocytes via gap junctions, which allows them to communicate with one another and presumably respond appropriately to mechanical stimuli (Stanley *et al.* 2007). It is likely that intra- and interfascicular cells within the tendon have different functions although this has not been shown and in general tendon cell phenotype is poorly defined.

Tenocytes are able to remodel the matrix by synthesising matrix molecules, including collagen and proteoglycans, and enzymes responsible for degradation, including matrix metalloproteinases (MMPs). Specific MMPs are able to degrade different components of the matrix, but their activity is tightly regulated by a number of mechanisms. These include the presence of tissue inhibitors of metalloproteinases (TIMPs), whether the molecules are in their active form and their location within the matrix (Nagase *et al.* 2006). Molecular matrix composition differs between the tendons in the equine forelimb; the mature SDFT has higher GAG, COMP and water content, and greater cellularity than the CDET (Batson *et al.* 2003; Birch *et al.* 2008b), which presumably contributes to the difference in mechanical properties. The SDFT has a less stiff matrix (lower elastic modulus) than the CDET (Batson *et al.* 2003).

Characteristics of tendon degeneration

Degeneration of the SDFT is characterised by discolouration of the central core region of the tendon (Fig 3). This is frequently seen at *post mortem* in horses that exhibit no clinical signs of tendon injury, such as lameness or swelling (Webbon 1977; Birch *et al.* 1998). Recent attempts to detect these early changes *in vivo* using ultrasonography were not able to predict SDFT injury, although where SDFT pathology was identified, an acute injury was more likely to occur (Avella *et al.* 2009). Abnormal colouration is accompanied by changes in matrix composition; the central core region has increased levels of GAG, *type III* collagen and cellularity, and decreased collagen-linked fluorescence (a marker of matrix age) compared to the peripheral region of degenerated tendon and the core of normal tendon (Birch *et al.* 1998). Similar

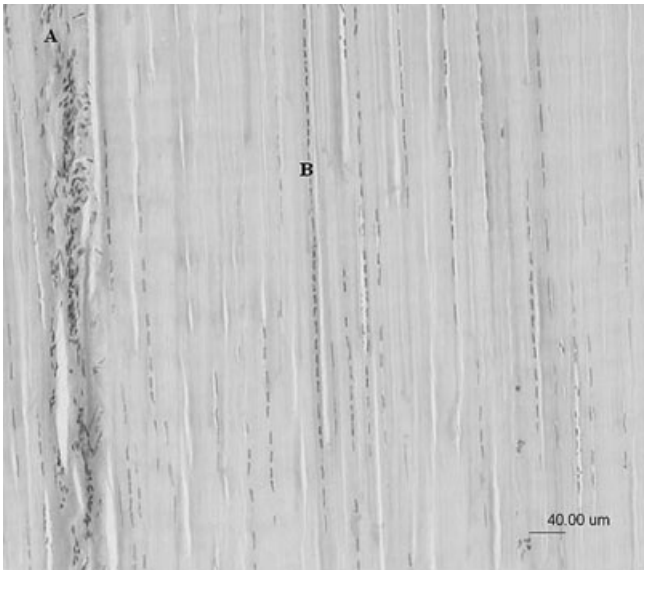

Fig 2: Longitudinal haematoxylin and eosin stained section of a normal mid-metacarpal region of equine SDFT showing areas containing interfascicular (A) and intrafascicular tenocytes (B).

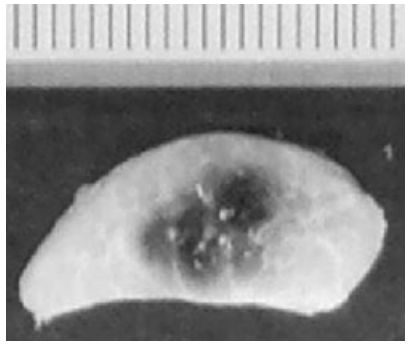

Fig 3: Mid-metacarpal region section of an injured SDFT showing central core discolouration.

changes occur in degenerated and painful human tendons, with upregulation of collagen *types I* and *III* (Ireland *et al.* 2001), increased production of inflammatory cytokines (Gotoh *et al.* 2001) and lower concentrations of molecules that are used as markers of matrix age (Bank *et al.* 1999; Riley *et al.* 2002) as common features.

Changes in gene expression and production of matrix degrading enzymes have also been reported; collagenase (MMP-1) expression and production increases in ruptured tendons, whereas stromelysin (MMP-3) is down-regulated (Riley *et al.* 2002; Jones *et al.* 2006; Clegg *et al.* 2007). The changes in matrix composition that occur with degeneration suggest an increased rate of matrix turnover, which may be an inadequate healing response or an inappropriate cellular response, resulting in the degradation of normal matrix. The stimulus for this change is not known but suggested causes include mechanically induced microdamage to collagen fibrils, hyperthermia, hypoxia or, in human tendons, a neurogenic aetiology has been suggested.

Microdamage to collagen fibrils

Localised damage can occur to the collagen fibrils when tendons are exposed to high strains as in the SDFT during high speed locomotion. *In vitro* experiments have shown that loading tendon fascicles at 80% of failure strain resulted in isolated fibrillar damage and fibril sliding (Lavagnino *et al.* 2006). This microdamage was accompanied by a localised increase in MMP-1 gene expression and production. The hierarchical structure of tendon is such that, during a loading cycle, some fibrils may experience higher strains and therefore be at higher risk of damage than others (Kastelic *et al.* 1978). This isolated fibrillar damage may not affect the tendon's gross mechanical properties, but may alter cell-matrix interactions (Arnoczky *et al.* 2008a). However, if the microdamage is not repaired by the tenocytes it will accumulate and may then result in clinical injury. It may be expected, therefore, that high strain tendons have a greater capacity for matrix repair than low strain tendons. Although the SDFT has a higher cellularity than the CDET, the cells in the CDET exhibit increased mRNA expression of *type I* collagen and collagenases, and there are higher levels of the cross-linked carboxy terminal telopeptide of *type I* collagen (ICTP), a marker of collagen degradation (Birch *et al.* 2008a), suggesting the potential for, and the rate of, matrix turnover is higher in the CDET than in the SDFT. It is unclear why tenocyte activity is lower in the SDFT when this tendon is at higher risk of microdamage, and there are 2 main hypotheses that need to be considered. Structures that require high mechanical strength to function, such as the SDFT, may be protected from remodelling as this would cause them to weaken transiently as the collagen molecules are degraded and replaced (Laurent 1987). The alternative hypothesis is that cell activity is compromised by changes to the cells' physiochemical or mechanical environment that occur during high speed exercise.

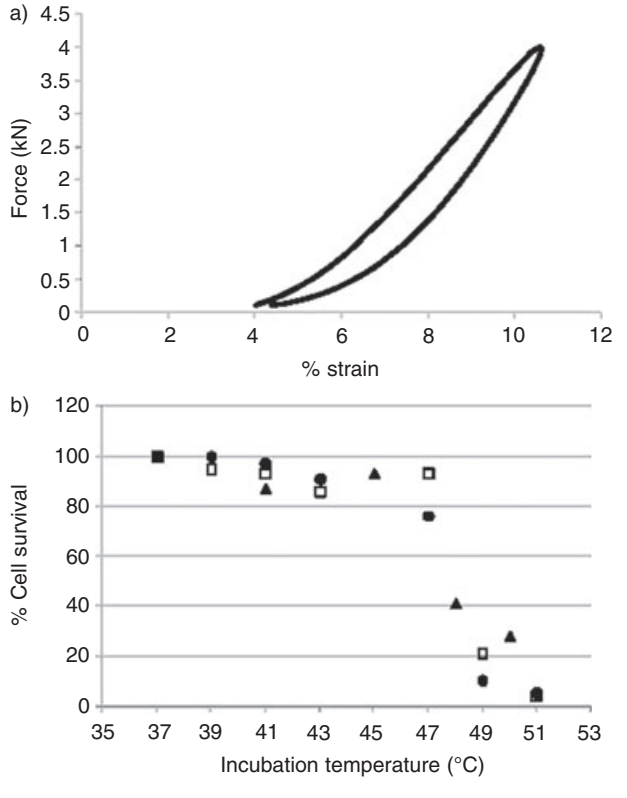

Fig 4: a) Hysteresis loop during cyclical loading and unloading of tendon. The energy lost is represented by the area within the loop. b) Equine tendon fibroblast survival following exposure to hyperthermia (10 min). Different symbols represent fibroblasts grown from different horses (data replotted from Birch et al. *1997a).*

Changes to physiochemical environment

Due to the viscoelastic nature of tendon, some of the energy stored by the SDFT is released as heat, rather than being returned as kinetic energy (Ker 1981), which causes the temperature of the tendon core to increase, and temperatures of 45°C have been recorded in the core of the SDFT *in vivo* during gallop exercise (Wilson and Goodship 1994). Although exposing most cell types to temperatures above the normal physiological range would result in cell death, tenocytes from the SDFT cultured *in vitro* in suspension have been shown to be heat resistant up to 48°C for a period of 10 min (Birch *et al.* 1997a) (Fig 4). However, cells may be more sensitive to heating *in situ* where they are able to communicate via their gap junctions (Burrows *et al.* 2009). Other studies have shown that above 45°C equine tenocytes produce more pro-inflammatory cytokines, which will increase the production of matrix degrading enzymes (Hosaka *et al.* 2006). No studies have measured temperature in the CDET *in vivo* but as this tendon experiences low strains and has a relatively small cross sectional area (mean ± s.d. CSA of 28 ± 7 mm^2 in the CDET compared to 96 ± 35 mm^2 in the SDFT; Batson *et al.* 2003) it is unlikely high temperatures would be reached. The poor blood supply in tendon contributes to the increase in temperature as the heat is dissipated relatively slowly, exposing the cells to high temperature for a longer period. The poor blood supply may also result in low oxygen levels in the tendon core which may further compromise cell activity. Tenocytes are capable of oxidative energy metabolism (Birch *et al.* 1997b), which suggests that their synthetic and degradative activity may be compromised by low oxygen levels.

Changes to mechanical environment

The mechanical deformation experienced by the cells within the SDFT depends on the coupling between the cell and extracellular matrix and this in turn affects cell activity. It has for example been shown that the strain experienced by individual cells is not the same as that applied to tendon fascicles (Screen *et al.* 2004). It is well

established that cells are able to respond to changes in their mechanical environment by altering synthesis and degradation of matrix components. This response was first documented in bone cells, which increase or decrease bone mass according to the amount of load placed on the bone. Frost (1987) proposed that osteoblasts have a pre-set sensitivity to deformation such that if strain-induced signals are above or below a certain level, termed the 'mechanostat set-point', the cells will remodel the matrix accordingly. Recently, it has been shown that tendon cells have a similar ability to remodel the matrix according to the strain they experience (Lavagnino and Arnoczky 2005). Cells sense matrix deformation by mechanotransduction, which converts a mechanical signal into a biological response. Receptors on the cell surface will detect deformation, and this information will be passed to the nucleus via the internal cytoskeleton, where the appropriate response will be initiated (Ingber 1997).

While physiological strains may be expected to result in tendon adaptation unusually high strains may result in a damage response. *In vitro* studies have shown that exposing tenocytes to high strains causes them to alter their production of specific proteins. Exposing human tenocytes to 3.5% cyclical strain at a frequency of 1 Hz for 2 h caused increased expression of MMP-3, which degrades proteoglycans, and interleukin 1-beta, (IL1-β) a cytokine that is able to induce expression of MMPs (Tsuzaki *et al.* 2003). Cyclically stretching human tendon cells from 4–12% at a frequency of 0.5 Hz caused an increased production of prostaglandin E_2, which is an inflammatory mediator of tendinopathy (Wang *et al.* 2003).

It has also been found that loading rabbit tenocytes at 5% cyclical strain with a frequency of 0.33 Hz causes increased expression of MMP-1 and MMP-3. However, this upregulation only occurred with the addition of IL1-β (Archambault *et al.* 2002). The strains used in these studies may not appear to be high relative to the strains seen by the SDFT in a galloping horse; however, it is difficult to recreate *in vitro* the strains experienced by cells *in vivo*. Visualising cells in fascicles exposed to 8% strain has shown that the local strain experienced by the cells does not appear to exceed 2% (Screen *et al.* 2004). Cells in these *in vitro* studies are, therefore, being exposed to strains equivalent to those that might be experienced *in vivo* in a high strain energy storing tendon such as the SDFT. These findings suggest that the strains experienced by the SDFT may cause cells to increase production of degradative enzymes that will break down the matrix, resulting in the degenerative changes seen in tendinopathy.

Alternatively, it has been proposed that it is the understimulation of cells rather than over-stimulation that causes the upregulation of matrix degrading enzymes. Microdamage results in the unloading of the damaged fibrils (Lavagnino *et al.* 2006), and fibril disruption will alter the cell-matrix interactions, which may result in the localised stress-shielding of some cells. Stress deprivation causes increased expression of the collagenase MMP-13, alterations in cell morphology and pericellular environment (Arnoczky *et al.* 2008b) and increased apoptosis (Egerbacher *et al.* 2007). It has also been reported that stress deprivation alters the cell's response to loading; cells in stress-deprived tendons that were then cyclically loaded were found to express significantly higher levels of MMP-13 mRNA than cells that had not been stress deprived (Arnoczky *et al.* 2008b). This suggests that understimulation causes the cells to alter their 'set point', so they may be unable to respond appropriately to mechanical stimuli and so will not repair any microdamage. The cells may also act to actively degrade the matrix, which may accelerate the rate of microdamage accumulation.

Abnormal loading events

Microdamage has been shown to occur *in vitro* after a single loading event at 80% of failure strain (Lavagnino *et al.* 2006). It is possible that during repetitive loading (i.e. during high speed exercise) one abnormal loading cycle may result in strains of a high enough magnitude to induce isolated microdamage without clinical injury (Arnoczky *et al.* 2008a). This abnormal loading may be as a result of muscle fatigue, changes in the neuromuscular response or exercise on an uneven surface (Kai *et al.* 1999). This suggests that tendon injury is more likely to occur towards the end of a race, when racing over longer distances or over fences, and this is supported by studies that have found increased tendon injury in these situations (Peloso *et al.* 1994; Williams *et al.* 2001; Pinchbeck *et al.* 2004; Takahashi *et al.* 2004). Recently, it has been proposed that the SDFT may be at increased risk of injury due to fatigue of the deep digital flexor muscle. During high speed locomotion, the DDFT stores little energy, but acts to stabilise the metacarpophalangeal joint during hyperextension. However, its corresponding muscle has a high percentage of fast twitch muscle fibres, and so is more susceptible to fatigue. If this occurs, the metacarpophalangeal joint will be destabilised and so the SDFT will be subjected to higher strains, which may result in fibril microdamage (Butcher *et al.* 2007).

Conclusions

High strains experienced by the SDFT undoubtedly contribute to the high incidence of injury. The findings of epidemiological studies support this as the forelimbs, which carry 60% of the horse weight when standing and even more when galloping, are more susceptible and activities that result in particularly high strains such as galloping and jumping at speed increase the risk of injury. However, the presence of degenerative matrix changes and the increased incidence with increasing age suggest that injury is not due to a simple mechanical overload. Furthermore some horses compete at the highest level and never suffer from tendon damage.

There is a large variation between individual horses in the strength and stiffness of the SDFT but it is not known at present whether this relates to injury susceptibility. The ability to turnover the matrix is likely to be important but as yet it is not clear why the capacity to do this should be less in the injury prone SDFT than the CDET. Other factors, such as hyperthermia and low oxygen tension, are relatively unexplored; nonetheless their contribution to tendon integrity could be significant. Understanding the variation in tendon matrix at the molecular and cellular level and the relationship to the unique requirements of individual tendons is the key to developing more effective treatment regimes and to reducing the incidence of injury through managing training practices.

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