Review

The influence of ageing and exercise on tendon growth and degeneration—hypotheses for the initiation and prevention of strain-induced tendinopathies


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Abstract

Strain-induced tendinopathy is a common injury in both human and equine athletes, with increasing incidence associated with greater involvement in sport and an increasingly aged population. This paper reviews our studies on the abundant non-collagenous protein, cartilage oligomeric matrix protein (COMP), in equine tendons. Its variation between tendon type and site, age and exercise has provided an insight into how age and exercise influence tendon growth and maturation. Tendons can be broadly divided into two types, reflecting their different matrix composition and function: the energy-storing tendons used for weight-bearing and locomotion, which suffer a high incidence of strain-induced tendinopathy, and positional tendons involved in limb placement or manipulative skills. It would appear that while energy-storing tendon can respond to the mechanical forces applied to it during growth, there is no evidence that it can do so after skeletal maturity. Instead, cumulative fatigue damage causes degeneration at the molecular level, potentially weakening it and increasing the risk of clinical injury. Appropriate exercise regimes early in life may help to improve the quality of growing tendon, thereby reducing the incidence of injury during ageing or subsequent athletic career.

Keywords: Tendon; Ageing; Exercise; Physiology; Degeneration; Tendinopathy; Cartilage oligomeric matrix protein (COMP); Matrix

1. Introduction

Strain-induced tendinopathy is an extremely common injury in human and animal athletes. Studies in man have shown a high incidence of injury in the Achilles tendon of professional athletes, while the incidence in the sedentary population is low (Gibbon et al., 1999). In horses, recent epidemiological studies have revealed an incidence in National Hunt horses (those horses that race over jumps) in training in the UK of 43% (Pickersgill, 2000) and 46% of injuries on racecourses being due to tendon strain injuries (Williams et al., 2001). These specific strain-induced injuries are associated with specific tendons, the Achilles and patellar tendon/ligament in humans, and the superficial digital flexor tendon (SDFT) of the forelimb in the horse (Fig. 1). These particular energy-storing tendons serve not...
Fig. 1. The normal anatomy of the equine distal limb. Note the relative positions of the superficial digital flexor tendon, which supports the metacarpophalangeal joint under weight bearing, and the common digital extensor tendon, which is a positional tendon and does not receive any weight-bearing load.

only to transmit muscle-generated force to bone to move joints, but more importantly, they act like springs to store elastic energy for energy-efficient locomotion (Alexander, 1988). Interestingly, other tendons that do not serve this physiological role, but instead act to position segments of the limbs primarily as a function of muscle contraction, such as the digital extensor tendon in the horse (Fig. 1) and the anterior tibialis and hand and arm tendons in humans, have a low incidence of strain-induced tendinopathy. Epidemiological data in both humans and man have shown a strong association between the incidence of strain-induced tendinopathy and both age and exercise (Gibbon et al., 1999; Pickersgill, 2000). With an increasing interest in exercise for cardiac and bone health in an increasingly ageing human general population, there has been an increase in the incidence of Achilles tendinopathy in both younger athletes and in the elderly in recent years (Moller et al., 1996; Houshian et al., 1998; Maffulli et al., 1999).

This difference in tendon-specific incidence of clinical injury implies a difference in the response of these two groups of tendons to physiological and biomechanical influences associated with age and exercise. Most musculoskeletal tissues accommodate changes in mechanical demand by undergoing functional adaptation involving alterations in mass and structural architecture. In the case of tendons, there have been relatively few studies to investigate the relationship between physiological demand and associated changes in molecular composition. Studies in miniature swine demonstrated a gross change in size in digital extensor, but not flexor tendons (Woo et al., 1982). This has been supported by studies in thoroughbred horses, which showed exercise-induced hypertrophy of the digital extensors, but not the energy-storing flexor tendons (Birch et al., 1999).

This difference between the two tendon types is reflected by differences in mechanical properties. The energy-storing tendons in both horses (Batson et al., 2000) and humans (Birch et al., 2001) show significantly lower elastic modulus than the positional tendons, which would support optimisation for their specific physiological roles.

Tendon comprises connective tissue characterised by cell populations within an extracellular matrix. The functional role of both the complete tendon and site-specific regions within a tendon is...
reflected in the molecular composition of the matrix. Thus, tendons exhibit anisotropy in matrix composition between regions loaded primarily in tension (‘tensile regions’, although also subjected to compression when stretched) and regions subjected to additional external compression when the tendon changes direction around a bony prominence (‘compressed regions’). The site-specific functional regions are reflected in terms of matrix composition, with the tensile regions containing a larger abundance of the species of small proteoglycan (the leucine-rich repeat proteins, such as decorin and fibromodulin), and the compressed regions having a more fibrocartilagenous phenotype, with the large proteoglycans of aggrecan and versican predominating (Vogel and Heinegard, 1985; Vogel and Koob, 1989; Evanko and Vogel, 1990; Vogel et al., 1994). This site-specific matrix composition has been shown to be linked to function by tendon transfer experiments in vivo (Gillard et al., 1979) and explant loading experiments in vitro (Koob and Vogel, 1987; Koob et al., 1992; Evanko and Vogel, 1993), suggesting some evidence for functional adaptation to these extremes of biomechanical environment.

Another non-collagenous protein recently found to be abundant in tendon is cartilage oligomeric matrix protein (COMP), a five-armed protein, bound via disulfide bonds at their N-termini and with globular C-terminal domains (Hedbom et al., 1992; Efimov et al., 1994) (Fig. 2). It is a large protein that can be visualised as a ‘bouquet’ with rotary shadowing electron microscopy (Mörgelin et al., 1992). Its precise function is unknown, although it has been shown to bind, via its globular C terminal domains, to fibrillar collagen molecules (Type I, II), as well as to more complex fibril-binding collagen IX, with a zinc-dependent mechanism (Rosenberg et al., 1998; Thur et al., 2001). This protein has proved an interesting component in tendon because of its restricted distribution within the body to those soft tissues for which the primary role is to resist load (tendon, ligament, cartilage, meniscus and intervertebral disc), which suggests it has a function in this role.

As further evidence of its importance in tendon, mutations in COMP have been shown to cause pseudoachondroplasia in man (Briggs et al., 1995; Hecht et al., 1995; Holden et al., 2001; Thur et al., 2001), which is characterised by short stature, early-onset osteoarthritis, and lax tendons and ligaments. Thus, the phenotype corresponds to the distribution of COMP, but this mutation would not appear to provide conclusive proof of the importance of COMP for tissue structural integrity, as it results in retention of the protein in the endoplasmic reticulum, thereby potentially disrupting the release of other matrix molecules.

Despite the evidence to suggest the adaptability of a site-specific matrix, the high incidence of injury, influenced by ageing, and a failure to show changes in size of the flexor tendons with exercise suggest dissociation between functional demand and matrix adaptation in energy-storing tendons. The horse is an ideal model with which to study the effects of age and exercise on these tendons, as it is a species that has phases of growth, maturation and ageing, while also being athletic. The superficial digital flexor tendon in the horse is subjected to very high loads—10–20 kN (1–2 t of weight; Goodship et al., 1994) on a structure that is approximately 100 mm² in cross-sectional area and 45 cm in length. In doing so, it stretches up to 16% in vivo during high-speed locomotion (Stephens et al., 1989), which is close to its failure strain (superficial digital flexor tendons rupture at between 12 and 20% in vitro; Goodship et al., 1994).

Since this particular tendon contributes to energetic efficiency in an animal evolved and further selectively bred for high-speed locomotion, it functions close to failure with a low safety margin. This may explain the extremely high incidence of partial rupture of this specific tendon. Once ten-
Tendons are injured, the slow process of repair with fibrous scar tissue occurs. This scar tissue is essentially the same as that forming in skin wounds and does not have the same matrix composition as the normal tendon. While, given time, this repair tissue can become mechanically strong (Crevier-Denoix et al., 1997), there is an increase in elastic modulus, and hence the tissue is compromised in functional efficiency. The high stiffness of scar tissue also puts increased strain on adjacent, relatively less injured and remote areas of the same tendon, resulting in a high incidence of recurrent injury—a common feature in both equine and human athletes. Prognosis for these injuries is largely dependent on the severity of the initial injury, with little contribution from the therapeutic regime subsequently applied. Current treatment modalities are primarily aimed at ‘educating’ the reparative tissue to be more functional, but none, at present, are able to regenerate normal tendon tissue. It is the authors’ belief that the greatest contribution to restoration of function is by a structured rehabilitation programme with appropriate monitoring. This imposition of a controlled functional stimulus has the potential to modulate the repair process in terms of both the structural morphology of the repair tissue and the molecular composition of the matrix.

Previous post mortem studies on equine tendon suggested that the SDFT had a preceding stage of sub-clinical damage that predisposed the horse to clinical injury (Webbon, 1977). This has been supported by the identification of ‘sub-clinical’ central discoloured regions of flexor tendons that appeared to be normal on clinical examination prior to euthanasia (Goodship et al., 1994). Subsequent analysis of similar tendons using more advanced modern ultrasound imaging can now detect these lesions. The injured tendon is enlarged, and matrix analyses of the red-stained central core lesions support the interpretation that scar tissue is present (high collagen III and glycosaminoglycans (Birch et al., 1998)). Notwithstanding this finding, Achilles micro-tears have been identified in asymptomatic professional athletes (Gibbon et al., 1999), and histological evaluation of rotator cuff tendons (Riley et al., 1994) and electron microscopy examination of tendons (Kannus and Jozsa, 1991) have both identified degenerative pathology, which, as in the equine SDFT, may precede overt clinical injury. Furthermore, many strain-induced tendinopathies in both human (Gibbon et al., 1994) and the horse (Webbon, 1977) are bilateral, which is inconsistent with a sudden onset injury with no prior pathology.

In support of the hypothesis that clinical tendinopathy is a consequence of preceding matrix degeneration are the epidemiological studies demonstrating a strong association with age (Gibbon et al., 1999; Pickersgill, 2000). Only small amounts of degeneration dramatically increase the risk of progression to clinical tendinopathy, because the tendon is operating close to its tolerance limits. Therefore, preventing such cumulative degeneration potentially has a large effect in reducing the incidence of tendon injury in a population of athletes.

Furthermore, we have hypothesised that age and exercise are synergistic in the adult horse in initiating tendon degeneration (Smith et al., 1999). Understanding the processes that control matrix composition in relation to mechanical pathophysiological influences will give us strategies with which we can potentially prevent tendon injuries.

This paper reviews our data on the effects of both age and exercise on tendon matrix composition, from which we propose rational strategies for the prevention of strain-induced tendinopathy.

2. General materials and methods

2.1. Exercise studies

2.1.1. Mature horses

Two exercise studies were performed, each with 12 thoroughbred fillies. These have been described in detail elsewhere (Patterson-Kane et al., 1997; Smith et al., 1999). In brief, for the first experiment (long-term study), five 21-month-old horses were exercised at high speed on a treadmill three times per week for 18 months before euthanasia (at 3 years 3 months of age). A control group of six horses was given only walking exercise during the same period.

In the second experiment (short-term study), similar treadmill exercise was given for 4.5 months to six horses from 19 months of age. Another control group of six horses of the same age was given only walking exercise.

2.1.2. Immature horses

Two individual clinical cases were analysed, as these had had non weight-bearing lameness on one limb for 6 weeks. The first case was a 5-week-old
foal that suffered a radial fracture, which was repaired with internal fixation. However, although the foal was ambulatory, it failed to bear weight on the affected limb for 6 weeks. At this point (at 11 weeks of age) it was euthanased because of the lack of clinical progress. The digital flexor and extensor tendons (and metacarpophalangeal joint cartilage) from both limbs were analysed for COMP.

In the second case, an 18-month-old horse suffered an infected elbow, which rendered it non-weight-bearing on one limb for a similar period (6 weeks). Euthanasia was performed at the end of this period because of the failure in elimination of sepsis and the associated hopeless prognosis. The digital flexor tendons were immediately recovered post mortem for COMP analysis.

In an exercise experiment on foals, 43 warm-blood foals were divided into three groups from 1 week of age. The exercise protocol has been described in detail elsewhere (van Weeren and Barneveld, 1999). In brief, Group 1 received restricted exercise (box rest), Group 2 was kept in a box, but given enforced, high-speed exercise for short periods for 5 days of the week (training), and Group 3 was allowed free exercise (pasture). Half of the foals were euthanased at 5 months of age and the remainder were grouped together and given low-level free exercise until they were 11 months old, when the remainder of the foals were euthanased. The digital flexor tendons were immediately recovered post mortem and analysed for COMP.

2.2. Tendon sample recovery from cadavers

The forelimb superficial digital flexor tendon and, in some cases, the common digital extensor tendon were immediately recovered post mortem from horses of known age euthanased for reasons other than tendon disease. Samples from the SDFT comprised of tensile (metacarpal) and compressed (metacarpophalangeal) regions. Only the metacarpal region of the common digital extensor tendon was used, since this tendon does not have any portion under compressive strain.

The tendons were either stored frozen for compositional analysis or divided fresh into small 2-mm cubes for tenocyte recovery by collagenase digestion. Tenocytes recovered in this way were cultured to confluence and passed for analysis of COMP synthesis in response to TGF-β and biaxial strain in the Flexercell apparatus (Buckley et al., 1988; Brown et al., 2000) with or without the presence of TGF-β.

2.3. Cartilage oligomeric matrix protein (COMP) analysis

A section of tendon (approximately 500 mg wet weight) was frozen in liquid nitrogen and ground in a tissue disintegrator (Retsch). In some cases, dry weights were first obtained by freeze-drying before grinding to give a measurement of hydration. For tendon ground without freeze-drying, 20 v/w of extraction buffer (4 M guanidine hydrochloride with protease inhibitors) was added to the frozen powder and extraction carried out at 4 °C for 24 h with continuous agitation. For the freeze-dried samples, 100 v/w of extraction buffer was used.

After 24 h, the supernatant was recovered by centrifugation. A 10-μl aliquot of this supernatant was twice precipitated in 95% ethanol/50 mM sodium acetate. After the second precipitation, the precipitate was dried and dissolved in sample buffer. Appropriate dilutions of the samples were made, determined from parallel inhibition curves, and the COMP in the sample was quantified in triplicate using a homologous inhibition ELISA as previously described (Smith et al., 1997), using purified equine COMP as plate coating, and standards and anti-equine COMP polyclonal antiserum as primary antibody. This assay has previously been shown to detect COMP at concentrations between 0.005 and 0.05 μg/ml. The COMP concentration in the extract was then used to calculate the COMP content of the tissue in mg/g wet weight.

3. Results

3.1. COMP variation with age (Smith et al., 1997)

Matrix analysis of these cadaveric tendons demonstrated considerable variation in COMP levels, both between tendon type and site, and with age. COMP levels were universally low in all tendons at birth (<1 mg/g wet weight), but increased in an exponential fashion as a function of age only within the tensile region of the digital flexor tendons, to peak at approximately 2 years (~10 mg/g wet weight). Thereafter, COMP declined to lower levels (~2 mg/g wet weight) after approx-
Fig. 3. COMP levels in tensile (metacarpal) and compressed (metacarpophalangeal) regions of the superficial digital flexor tendon (SDFT) in the horse. The tensile region shows an almost exponential increase up to 2 years of age, and thereafter falls precipitously. In contrast, the compressed region shows a more gradual rise to lower levels that are maintained. The common digital extensor tendon (CDET) over the same age range is largely unchanged at the same level as in the neonate flexor tendons (long dashed line; E. Batson, personal communication).

Fig. 4. COMP levels in the tensile region of the superficial digital flexor tendon of the horse following intensive treadmill exercise (E) or just walking (controls, NE). The light-grey bars refer to the first experiment, when 18 months of exercise was given and the horses were over 3 years at the time of analysis; the dark-grey bars refer to the second experiment, when a shorter period of exercise was given and the horses were only 2 years old when analysed. Compare these ages with Fig. 3. There was a significant decrease in COMP levels with exercise in comparison to the controls (Fig. 4).

3.3. Exercise studies

3.3.1. Mature horses (Smith et al., 1999)

No significant alterations between exercised and control groups were observed for COMP levels in the short-term study when the horses were euthanased after 4 months of exercise at 2 years of age. In contrast, the horses given 18 months of exercise (3 years old at euthanasia) had a lower level of COMP, as would be predicted from the cadaveric data, but also showed a significant decrease in COMP levels with exercise in comparison to the controls (Fig. 4).

3.3.2. Immature horses

In the foal with non-weight-bearing on one limb for 6 weeks at 5 weeks of age, there was considerably higher levels (four-fold) of COMP in the weight-bearing tendons (and articular cartilage) in comparison to the non-loaded limb. In contrast, the digital extensor tendons, which normally have low levels of COMP, showed no difference in COMP levels. However, in a similar situation in a near-adult horse, when COMP has already accumulated in the tendon, there was little effect of reduced loading (Fig. 5).

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In the exercise study on foals, COMP levels were significantly lower in the foals given forced
exercise in comparison to those at pasture at 5 months of age (Fig. 6) (Cherdchutham et al., 1999). Following a further 6 months of lower-intensity exercise, although there was a similar pattern to the COMP levels between groups, there were no longer any significant differences.

3.4. Mechanism of COMP accumulation: the influence of growth factors

Tenocytes showed a dose-dependent increase in COMP production with TGF-β isoforms (1, 2 and 3) (Fig. 7). This effect was greater than that of mechanical load, which had a synergistic effect on COMP synthesis.

Tenocytes recovered from digital flexor tendon showed a greater COMP synthetic response than cells from extensor tendons (Goodman et al., 2000). Immature flexor tenocytes appeared to synthesise greater amounts of COMP than mature flexor tenocytes or extensor tenocytes from any age, although the latter group were still able to synthesise appreciable amounts of COMP (Goodman et al., 2000).

4. Discussion

Together with a recent finding demonstrating that the COMP promoter is most active in tendon and ligament (Deere et al., 2001), the finding that COMP is most abundant in the tensile region of energy-storing tendons in young animals indicates that the presence of this protein is unrelated to any cartilage phenotype.

The positive correlation of COMP levels with ultimate tensile strength and stiffness in equine digital flexor tendons at skeletal maturity suggests that COMP is in some way linked to the formation of a strong tendon matrix. Mechanical analysis of cadaveric tendons has shown a large (up to two-fold) variation in mechanical, structural and material properties within a given population, with no significant difference between tendons from left and right limbs within individual animals (Birch et al., 2000). This suggests that some individuals have developed weaker tendons than others, and that it is possible that these individuals are most susceptible to tendinopathy.
Fig. 6. COMP levels in the tensile (metacarpal) region of the superficial digital flexor tendon in growing foals at 5 (5m) and 11 months (11m) of age. The foals were given three different exercise regimes: box rest (maintained in a stall, with only minimal exercise); training (maintained in a stall, but given short periods of intense, enforced exercise); and pasture (maintained out at pasture, where natural regular self-exercise occurs). After 5 months, the foals were grouped together and given lower levels of exercise to determine if any deleterious effects of the enforced training would resolve. There was a significant decrease in COMP levels between the pasture and trained groups at 5 months. No significant differences were observed at 11 months.

The maximum accumulation of COMP during tendon development and subsequent loss after growth is finished would suggest that its main function is in the formation of tensile tendon matrix. As the C-terminal domain of COMP binds to a collagen molecule at four points equally distributed along the collagen molecule (Rosenberg et al., 1998), the five-armed structure of COMP acts to align collagen molecules and assist in early events in collagen fibrillogenesis (Rosenberg, Mörgelin and Heinegård, unpublished data). This has led to the speculation that COMP facilitates the early stages of collagen fibril formation in tissue. Adequate levels of COMP may therefore be necessary for the formation of a structurally competent collagen matrix. Thus COMP appears

Fig. 7. Dose response for digital flexor and extensor tenocytes (n=3; from neonatal tensile tendon) of COMP synthesis with addition of TGF beta 1. Note the increased COMP synthesis by tenocytes derived from the digital flexor tendon in comparison to those from the digital extensor tendon.
to be most highly expressed in those tissues synthesising matrix designed to withstand the largest tensile (or compressive) forces.

The data reviewed and presented in this paper are consistent with the energy-storing tendon having two phases in its life—a growth phase and an ageing phase. At birth, the tendon appears to be ‘blank’—i.e. homogeneous throughout its length and unadapted to load-bearing, in a similar fashion to that suggested for cartilage (Little and Ghosh, 1997; Brama et al., 2000). Site-specific variations related to external compressive forces have also been shown to develop after birth (Vogel and Heinegård, 1985; Vogel and Evanko, 1987). During growth, the tendon accumulates tendon matrix (as illustrated by COMP), which is modulated by the biomechanical environment. Appropriate exercise therefore appears to be necessary to stimulate optimal tendon development, although the tendon may also be potentially more easily injured during this phase if the loading/exercise is excessive. In support of this, enforced exercise in foals resulted in lower COMP levels at 5 months and reduced DNA and polysulfated glycosaminoglycans after 11 months compared to the restricted or free exercise groups (Cherdchutham et al., 1999). Other matrix analyses in these growing tendons have provided further evidence that a combination of immobilisation and enforced exercise appears more damaging to developing tendon than more regular, limited or free exercise (Cherdchutham et al., 1999).

During growth, growth factors potentially act synergistically with load to stimulate tendon matrix synthesis. The distribution of TGF-β isoforms in equine tendon shows an age-dependent distribution, with these isoforms being distributed throughout the tendon fascicles and endotenon during growth. However, after skeletal maturity, the immunohistochemical staining pattern changes, with TGF-β becoming solely located within the endotenon septa separating the tendon fascicles (Cauvin et al., 2000; Cauvin, 2001). However, while energy-storing tendon can potentially adapt to loading (exercise) during growth, it has little ability to do so after skeletal maturity. After this period, this type of tendon appears to age, with the loss and/or disruption of matrix—a change which is accelerated by exercise. The persistence of COMP levels in the compressed regions of the digital flexor tendons is consistent with matrix synthesis still being active in these regions during life. This observation in equine tendon correlates very well with the gene expression data for a variety of matrix proteins determined for different regions of bovine digital flexor tendons at different ages (Perez-Castro and Vogel, 1999). In this study using in situ hybridisation, gene expression was evident in all areas of the tendon during growth and in the adult compressed tendon, but absent from adult tensile tendon.

After skeletal maturity, the energy-storing flexor tendon appears to cease matrix synthesis and is poorly, if at all, responsive to loading/exercise. Exercise given during this phase serves only to accelerate the ageing effect of accumulating micro-trauma, resulting in tendon matrix degeneration.

This hypothesis is supported by other analyses of these tendons. Collagen fibril analysis has shown an increased predominance of small-diameter fibrils in the central core region of the long-term exercised group (Patterson-Kane et al., 1997). While this could represent the formation of new collagen, there was no significant increase in tendon size or collagen content, and the collagen ‘age’ determined by autofluorescence of non-enzymatic glycation products was not significantly different between the two groups. Both these findings suggest that exercise causes disruption of the collagen and non-collagenous matrix, rather than adaptive hypertrophy.

This may appear contra-intuitive, as other skeletal tissues, such as muscle and bone, have been shown to dramatically respond to load. However, it is now known that, at least, the bone response is also very age-dependent, with the highest activity during puberty and the lowest activity in the aged. As the SDFT of the horse has to essentially function as a spring to store energy on loading, tissue stiffness is critical for optimising this function. Too stiff or too elastic a ‘spring’ would make it less efficient for the given weight of animal. It is therefore possible that, once an optimised tendon is formed at skeletal maturity, there is a much-reduced need to synthesise further matrix, and so the synthetic machinery is ‘turned off’.

The control of expression of genes for the matrix protein composition in the tendon during growth, exercise and ageing is not clear. The low level of matrix synthesis could be a consequence of cellular senescence, loss of mechanotransduction, or growth factor stimulus. Allied studies in our laboratories have shown that immunohistochemical staining of the prototypic anabolic growth factor,
TGF-β, is lost from tendon fascicular tissue after skeletal maturity. Furthermore, there is no detectable TGF-β gene expression after birth (Cauvin et al., 2000; Cauvin, 2001). These findings are most consistent with a mechanism more related to the absence of necessary growth factors than the absence of cellular synthetic ability, although a reduction in cell activity and the loss of a co-ordinated mechanotransduction response (such as the loss of gap junctions between cells) could also contribute (McNeilly et al., 1996). Should the major influence on the synthetic ability of the tendon be the lack of appropriate growth factors, this presents a possible therapeutic target for the prevention of tendon degeneration.

The mature tendon normally endures the natural life-style of the horse. It ages and accumulates micro-damage, but only to levels that would not endanger the functional competence of the tissue. However, the artificial superimposition of increased exercise on this ageing mechanism (through training and racing horses, or increased athleticism and longevity in man) potentially accelerates this degenerative process to weaken the tissue sufficiently to allow the initiation of clinical tendinopathy when loads overcome the functional capacity of the tendon.

There are several potential candidates for a mechanism of matrix degeneration. These include direct matrix damage from physical forces, hyperthermia of tendon tissue caused by energy lost as heat through hysteresis (Wilson and Goodship, 1993) and relative hypoxia (Strömberg and Tufvesson, 1969; Kannus and Jozsa, 1991; Jarvinen et al., 1997), all of which could either act directly on the matrix or on tenocytes to cause a release of destructive proteolytic enzymes.

From the results of these studies, the following hypothesised strategies for the prevention of strain-induced tendinopathies can be proposed.

1. Maximise the quality of tendon prior to skeletal maturity with:
   – Early introduction of controlled exercise regimens with appropriate monitoring (Fig. 8).
   The exact level quantity and intensity of exercise necessary is currently unknown, but a ‘window’ of opportunity in both time and amount/intensity probably exists. If tendon, at this stage, responds in fashion similar to bone, then relatively short periods of high and diverse strain rates would be most appropriate. It is interesting to speculate that the normal gambolling activity of young foals at pasture, which includes a large amount of prancing jumps, may be perfectly designed for this function.
   – Improved genetic determinants.

2. Reduce the degeneration after skeletal maturity:
   – Avoid training directed at tendon adaptation in the adult, as it will serve only to accelerate degeneration, and hence long periods of high peak loads should be avoided.
   – Prevent the cumulative microdamage in adult tendon by identifying and preventing the processes involved (e.g. the release of proteolytic enzymes).
   – Reactivate resident cell populations to repair microdamage, or at least re-activate matrix synthesis.

3. Reduce the risk factors for provoking clinical tendinopathy (e.g. high peak loads caused by incoordination caused by fatigue, hard ground surfaces on which the horse is running, etc.).

We are currently evaluating the first of these strategies in vivo. We have been able to demon-
strate a significant increase in the rate of increase in SDFT cross-sectional area with a short period of additional exercise from 3 to 15 months of age (Kasashima et al., in press). Matrix analysis will be needed to confirm that this change is true adaptation rather than injury or abnormal matrix composition.

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