Role of Mechanobiology in the Pathogenesis of Tendinopathy: Lessons Learned From Horses and Humans

Steven P. Arnoczky, DVM

Author's address: Laboratory for Comparative Orthopaedic Research, College of Veterinary Medicine, Michigan State University, East Lansing, MI 48824; e-mail: arnoczky@cvm.msu.edu. © 2008 AAEP.

1. Introduction
Tendinopathy is a major clinical problem associated with sports and physical activity. In racehorses, tendinopathy is a cause of significant economic loss to the racing industry, with the incidence of tendon pathology in populations of racehorses ranging reported to be as high as 46% of all racetrack injuries. In humans, a similarly high incidence of Achilles tendinopathy in runners (between 24% and 64% annually) has been reported. Despite the increasing incidence of tendon problems in both horses and humans, very little is understood about the etiology of tendinopathy. The often chronic and debilitating nature of this condition and the failure of the repair process to completely restore normal tendon structure underscores the importance of understanding the etiopathogenesis of tendinopathy. Identifying the precise events associated with the etiology of tendinopathy could allow for early recognition of the “at risk” population and active intervention before the onset of debilitating symptoms or tendon rupture.

Despite the vast amount of information available regarding the pathologic progression of tendinopathy in both humans and horses, the exact pathogenesis of chronic tendinopathy remains largely unknown. Although numerous etiologic theories, including hypoxia, ischemia/reperfusion, reactive oxygen species, hyperthermia, systemic corticosteroid therapy, fluoroquinolone therapy, genetic collagen abnormalities, and a host of metabolic diseases have been forwarded as potential mechanisms of tendinopathy, the scientific background for most of these suggestions is lacking.

The traditionally accepted view of the pathogenesis of tendinopathy is that of a tendon injury that is associated with overuse. In this scenario, repetitive mechanical loading of the tendon initiates a cascade of catabolic events that eventually leads to tendon degeneration. Although this “mechanical strain” theory has been widely accepted as a plausible explanation for the etiological stimulus responsible for tendon overload injuries, the precise mechanisms by which mechanical strain can negatively impact tendon cell function are unclear. Recently, several laboratories have explored the role of mechanotransduction/mechanobiology in the etiopathogenesis of tendinopathy.
2. Mechanotransduction/Mechanobiology

The ability of tendon cells to sense and respond to load is central to the concept of mechanotransduction and mechanobiology and the subsequent maintenance of tendon homeostasis.\textsuperscript{11–13} Tendon cells can sense load through a complex mechano-electrochemical sensory system(s) that detects mechanical load signals through their interactions with the extracellular matrix and the resulting deformation of the cellular membrane and/or the cytoskeleton.\textsuperscript{10,11,14–18} The cellular deformation that occurs in association with extracellular matrix strain produces tension in the cytoskeleton, which can be sensed by the cell nucleus through a mechano-sensory tensegrity system to elicit a metabolic response.\textsuperscript{10–12,14,15,17–19} Although the precise level (magnitude, frequency, and duration) of mechanobiological stimulation required to maintain normal tendon homeostasis is not currently known, it is very likely that an abnormal level of stimulation may play a role in the etiopathogenesis of tendinopathy.\textsuperscript{7,8,19,20}

A proposed algorithm for the onset of overuse tendinopathy involves altered cell–matrix interactions in response to repetitive loading.\textsuperscript{21} In this scenario, repeated strains below the injury threshold of the tendon induce degenerative changes in the tendon–matrix composition and organization.\textsuperscript{20,22,23} The degeneration of the extracellular matrix leads to a transient weakness of the tissue, making it more susceptible to damage from continued loading. This damage accumulates until the overt pathology of tendinopathy develops.\textsuperscript{21} Although this is a feasible algorithm for the development of overuse tendinopathy, the precise mechanisms that lead to altered cell–matrix interactions have not been described.

Several investigators have theorized that it is the tendon cells’ mechanobiological response to over-stimulation secondary to repetitive loading that initiates the degenerative cascade that leads to tendinopathy.\textsuperscript{24–29} Although overstimulation of tendon cells in vitro has been shown to induce increases in inflammatory cytokines and degenerative enzymes,\textsuperscript{24–29} many of these studies have used non-physiologic strain patterns\textsuperscript{21,28} (excessively high strain amplitudes and/or frequencies, as well as long durations) or the addition of external factors\textsuperscript{26} to elicit these cellular responses. Thus, the clinical relevance of these studies must be called into question.\textsuperscript{8} In addition, no overstimulation model (in vitro or in vivo) has been able to reproduce the entire complex of pathologic events documented in chronic cases of tendinopathy.

3. Pathological Changes Associated With Tendinopathy

An increasing body of clinical material has suggested that tendons from tendinopathy patients exhibit an increase in catabolic enzymes (matrix metalloproteinases [MMPs]) as well as an induction of apoptosis (programmed cell death).\textsuperscript{2,5,23,30–41} A clinical study examining MMP activity in ruptured human tendons showed an altered expression and activity of several members of the MMP family.\textsuperscript{37} MMP-1 levels were significantly higher in ruptured tendons compared with normal controls, whereas MMP-2 and 3 levels were reduced, possibly representing a failure in the normal remodeling process.\textsuperscript{36,37} This increase in collagenase activity was associated with a deterioration in the quantity of the collagen network. Increased expression of MMP-1 was also found in human patellar tendinopathy tissue.\textsuperscript{31}

The result of this MMP-mediated degradation of the extracellular matrix is reflected in the histopathologic findings in tendinopathy that showed an irregular collagen orientation, collagen fiber disruption, change in collagen fiber diameter, a decrease in the overall density of collagen, and an up-regulation of collagen type III production.\textsuperscript{22,42,43} Another study that examined the histopathology of ruptured and tendinopathic Achilles tendons suggested that, although the ruptured tendons were significantly more degenerated than the tendinopathic tendons, the general pattern of degeneration was common to both groups.\textsuperscript{44}

In addition to the documented increase in collage

nase activity seen in clinical cases of tendinopathy, other studies have suggested that apoptosis may also play a role in the pathogenesis of tendinopathy in both horses and humans.\textsuperscript{32,40,41} Studies on the pathogenesis of rotator cuff disorders in humans have shown a significant increase in the number of apoptotic cells detected in degenerative supraspinatus tendons compared with normal control tendons.\textsuperscript{39,40} It is theorized that the increased number of apoptotic cells seen in the degenerative tissues of tendinopathy patients could adversely affect the rate of collagen synthesis and the potential for repair.\textsuperscript{41} Apoptosis was also detected in samples of inflamed superficial digital flexor tendons in the horse, possibly resulting in tendon weakness and an increased risk of tendinopathy.\textsuperscript{32} However, at present, it is still unknown whether apoptosis is the result or the cause of tendon degeneration.

Thus, although the pathologic responses seen in tendinopathy are well documented, to date, there is insufficient evidence to provide a direct link between the loading conditions experienced by a tendon during repetitive strain and the development of these pathologic changes.\textsuperscript{45}

4. Mechanobiology and the Etiopathogenesis of Tendinopathy

In an effort to explore the potential role of mechanobiology in the etiopathogenesis of tendinopathy, our laboratory has performed a series of studies to examine the response(s) of tendon to extracellular matrix strain.\textsuperscript{46–50} What we found was that tendon cells seem to be programmed to sense various levels of mechanical strain. At a specific level of strain,
termed the “mechanostat set-point: after a similar observation in bone cells," tendon cells are able to maintain a homeostatic level of gene expression. However, when tendon cells experience a mechanistic strain in excess of this "set-point," an anabolic response is stimulated. Conversely, when the level of mechanical strain drops below the "set-point," a catabolic response is stimulated. Indeed, loss of homeostatic strain in tendon cells in situ has been shown to stimulate a catabolic cascade of events that produces the classical pathologic features of tendinopathy. These observations have led to the theory that the destructive mechanism(s) that precedes overt pathologic development of tendinopathy may, in fact, be a catabolic response of the tendon cells to the local loss of homeostatic strain as a result of isolated, microscopic, collagen fiber damage.

Previous biomechanical studies have suggested that isolated collagen fibril damage occurs near the end of the linear portion of the load deformation curves of ligaments and tendons. The ability to produce isolated fibril failure within an otherwise intact tendon is likely attributable to the multi-compartmental structure of the tissue. The sequential straightening and loading of cramped collagen fibrils, as well as interfibrillar sliding and shear between fibers and/or fibrils, produce a non-linear, load-deformation behavior of tendons that may put certain fibrils “at risk” for damage before others. Using confocal laser microscopy and a previously described in vitro tensile loading apparatus, our laboratory has been able to show that isolated collagen fibril damage does occur in tendons in response to increasing tensile loads. As previously predicted, this damage occurs well in advance of complete tendon rupture. Although such damage may not affect the ultimate tensile strength of the tissues, it could alter the cell–matrix interactions within the damaged portion of the tendon. A previous study has shown that, after isolated fibril damage in tendons, the damaged fibrils relax. This would suggest an inability of these damaged fibrils to transmit load and therefore maintain a homeostatic mechanobiological stimulus to those cells associated with the damaged fibrils. Recently, our laboratory has shown that creation of isolated tendon fibril damage within an otherwise intact tendon fascicle results in an up-regulation of collagenase mRNA expression and protein synthesis by only those tendon cells associated with the damaged fibrils. This would suggest a loss of load-transmitting function in the damaged fibril(s) and a subsequent altered cell–matrix interaction within the affected area. The presence of increased levels of collagenase protein in these injured tendons is similar to what has been reported in clinical cases of tendinopathy.

Based on the above findings, our laboratory has forwarded the hypothesis that an alteration of cell–matrix interaction secondary to isolated fibril damage could result in a mechanobiological understimulation of tendon cells, which has been shown to result in an up-regulation of collagenase mRNA expression and protein synthesis. This, in turn, causes an initial degeneration of the pericellular matrix that may further compromise cell–matrix interactions and mechanobiological signaling. The degenerative process progresses throughout the extracellular matrix, resulting in a decrease in the material properties of the tendon. These changes could put more of the extracellular matrix at risk for further damage with subsequent loading. When a critical level of damage has been reached, the clinical and histologic signs of tendinopathy may become evident.

5. Clinical Relevance

As we have shown in our model system, a single high load event was able to cause sufficient fibril damage to initiate a cell-mediated response as a result of mechanobiological understimulation. Tendon micro-trauma can also result from a non-uniform stress occurring within a tendon producing abnormal loading concentrations and localized fiber damage. Therefore, it is possible that, during a series of repetitive loading cycles, a single abnormal loading cycle could produce strains sufficient enough to induce isolated fibril damage but not cause clinical injury. This abnormal loading cycle could be a result of muscle fatigue and/or altered kinematics that can occur with the performance of repetitive activities.

In the clinical situation, it has been documented that, in galloping horses, tendon strain can reach 80% of the tensile failure strain. Although these strain levels are similar to those reported to cause isolated fibril damage in both ligaments and tendons, they did not affect the ultimate tensile properties of the injured tendon. This fact, coupled with the observation that the central core fibrils of the equine superficial digital flexor tendon experience a higher strain level than do the peripheral fibers, would suggest that these fibrils are at risk for micro-damage during an overload event. This could explain the predilection for the core lesion in superficial digital flexor tendinopathy.

The idea that tendinopathy may, in fact, be initiated by a single overload event and is not a result of cumulative, repetitive activity is still controversial. However, a study that assessed risk factors for injury to the superficial digital flexor tendon and suspensory apparatus in Thoroughbred racehorses in New Zealand concluded that there was no evidence of an association between injury and cumulative high-speed exercise. Thus, while repetitive loading, per se, may not be responsible for initiating the cascade of events that lead to tendinopathy, it is likely that continued loading of the compromised tissue plays a significant role in the progression of the pathologic process. Additional research is needed to determine the magnitude of tendon forces experienced in activities that are associated with the development of tendinopathy. In addition, the effect of muscle fatigue and/or altered kinematics on
these tendon forces must be determined to gain insight into the mechanobiological mechanism(s) that may play a role in the etiopathogenesis of tendinopathy in both horses and humans.

The challenge will be to identify “at risk” individuals who have experienced these overload events so that rest, altered training regimens, or even proposed interventional therapies such as the use of MMP inhibitors may be initiated to minimize, or even inhibit, the progression of the catabolic cascade within the damaged tendon. Such approaches may allow the microdamage within the extracellular matrix of the tendon to undergo repair and re-establish the normal, homeostatic, mechanobiological environment for the tendon cells.

References


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