J Musculoskel Neuron Interact 2003; 3(4):326-328

Perspective Article

Hylonome

Tendon micromechanics and research methods in tendinopathy

J. Archambault

Women's Health & Bone, Wyeth Research, Cambridge, MA, USA

Keywords: Tendon, Tendinopathy, Fatigue Loading, Overuse Injury

Tendons are essentially built for life. Once adulthood is reached, tendons stop growing in length and cross-sectional area. For most people, their tendons last them for a lifetime[1]. However some people experience tendon pain (tendinitis or tendinopathy) with work or exercise-related activities, and in extreme cases, their tendon ruptures spontaneously.

Tendons have a built-in safety margin: the muscle it is attached to, even if maximally activated, can only load the tendon to 10-25% of its ultimate tensile strength. But then why do tendons suddenly rupture? It has been shown that 92% of ruptured tendons have degenerative changes in the matrix substance[2]. Ruptures are the end-stage of the degenerative process. In a normal situation, the weak point of a bone-muscle-tendon-bone unit is the interface between the muscle and tendon (myotendinous junction, where many muscle "pulls" occur). For a tendon to suddenly fail, it must have become weaker than the strength of this interface.

How might this weakness occur? In the case of inert construction materials, cyclic loading is a significant input – the repeated application of sub-maximal forces will eventually lead to a fatigue failure. If we define tendon ruptures as the fatigue failure of a tendon, then we can hypothesize that tendinopathies are the accumulation of fatigue or microdamage in the matrix, manifested as pain. Damage to our tendons probably occurs every day as the result of walking, running, lifting and other activities. However, tendons have an advantage over steel beams and concrete blocks because they are living structures with cells. These cells can repair the damage to return the tendon to an undamaged state[3]. Over the period of months and years, un-repaired damage may result in a catastrophic failure (tendon rupture). But since not every person who runs experiences tendon pain or rupture, there must be tremendous individual variation in the biology (repair capacity) of the tendon.

Unfortunately little experimental data exists to support this hypothesis. Microdamage has never been shown to occur *in vivo* with repeated loading; it has been demonstrated *in vitro* during fatigue testing[4]. We also don't know if microdamage is a stimulus for the cells to remodel or repair the matrix. Do tendon cells have a way to evaluate the integrity of the matrix around them? Changing the tension on the cytoskeleton of a tendon cell has been shown to induce collagenase expression in *ex vivo* systems[5]. This suggests that tendon cells have a set-point of "normal" tension, and that alterations to this set-point trigger a biological response.

How could research into tendon microdamage further our understanding of tendinopathy mechanisms? Animal models with controlled loading inputs have failed to produce degenerative changes in the tendon matrix (Table 1). A feasible alternative would be an *ex vivo* organ culture system with loading inputs[6,7]. It may be possible to reproduce the tendon degeneration process with long-term experiments. Tendons could be loaded to various portions of their fatigue life and the remodeling response measured (matrix synthesis or degradation). One could then determine how long it takes to repair a certain amount of damage, and if there is a threshold over which the damage cannot all be repaired. Once information is available about the natural capacity of the cells to repair damage, pharmacological modulation (i.e., addition of growth factors) could be evaluated to treat this disease or prevent its progression.

The author has received corporate appointments with Wyeth.

Corresponding author: Joanne Archambault, Ph.D., Staff Scientist, Wyeth Research, 200 CambridgePark Drive, Cambridge, MA 02140, USA
E-mail: jmarchambault@wyeth.com

Accepted 1 August 2003

References

1. Frost HM. Skeletal structural adaptations to mechanical usage (SATMU): 4. Mechanical influences on intact fibrous tissues. Anat Rec 1990; 226:433-439.
2. Jozsa L, Reffy A, Kannus P, Demel S, Elek E. Pathological alterations in human tendons. Arch Orthop Trauma

Reference	Animal	Target Tendon	Means	Result
Rais 1961 Acta Chir Scand Suppl 268:1	Rabbit	Achilles	Acute muscle stimulation	Paratenon inflammation
Backman et al. 1990 J Orthop Res 8:541-7	Rabbit	Achilles	Chronic muscle stimulation	Paratenon inflammation and tendon degeneration
Archambault et al. 2001 Conn Tissue Res 42:13-23	Rabbit	Achilles	Chronic muscle stimulation	No changes
Smutz et al. 1994 Clin Biomech 9:15-20	Monkey	Wrist flexors	Chronic muscle stimulation	No changes
Soslowsky et al. 2000 J Shoulder Elbow Surg 9:79-84	Rat	Supraspinatus	Chronic treadmill running	Tendon degeneration and decline of mechanical properties
Lai et al. 1995 2nd Comb ORS p. 322	Chicken	Gastrocnemius	Ablation overload	Less collagen material
Han et al. 1995 Trans ORS, p. 610	Rabbit	Lateral common extensor	Acute muscle stimulation	Partial failure at lateral epicondyle
Messner et al. 1999 Cells Tissues Organs 165: 30-39	Rat	Achilles	Chronic muscle stimulation	Paratenon inflammation
Sakata et al. 1988 Rheumatol Int 8:47-53	Rabbit	Tibialis anterior	Antigen injection	Inflammation of synovial sheath
Williams et al. 1984a, 1984b Res Vet Sci 36:326-338 (a) Conn Tissue Res 12:211-227 (b)	Horse	Superficial digital flexor	Single collagenase injection	Acute inflammation, disruption of matrix, more type III collagen & fibronectin
Soslowsky et al. 1996 J Shoulder Elbow Surg 5: 383-392	Rat	Supraspinatus	Single collagenase injection	Disruption of matrix, hypercellularity
Sullo et al. 2001 J. Orthop Sci 6:349-357	Rat	Achilles	Chronic PGE_1 injection	Inflammation & fibrosis in paratenon, tendon degeneration
Stone et al. 1999 J Orthop Res 17:168-177	Rabbit	Patellar	Collagenase injection Cytokine injection	Disruption of matrix, hypercellularity
Shakibaei et al. 2001 Arch Toxicol 75:97-102	Rat	Achilles	Oral fluoroquinolone antibiotics	Degenerative alterations, loss of cell-matrix interactions

Table 1. Summary of animal models of tendinopathy - modified from Archambault & Banes[8].

Surg 1990; 110:15-21.
3. Schechtman H, Bader DL. *In vitro* fatigue of human tendons. J Biomech 1997; 30:829-835.
4. Schechtman H, Bader DL. Fatigue damage of human tendons. J Biomech 2002; 35:347-353.
5. Lavagnino M, Arnoczky SP, Tian T, Vaupel Z. Effect of amplitude and frequency of cyclic tensile strain on the inhibition of MMP-1 mRNA expression in tendon cells: an *in vitro* study. Connect Tissue Res 2003; 44:181-187.
6. Hannafin JA, Arnoczky SP, Hoonjan A, Torzilli PA. Effect of stress deprivation and cyclic tensile loading on the material and morphologic properties of canine flexor digitorum profundus tendon: an *in vitro* study. J Orthop Res 1995; 13:907-914.
7. Ker RF, Wang XT, Pike AV. Fatigue quality of mammalian tendons. J Exp Biol 2000; 203:317-327.
8. Archambault JM, Banes AJ. Research methodology and animal modeling in tendinopathy. In: Maffulli N, Renstrom P, Leadbetter W (eds) Tendinopathy: Basic Sciences and Clinical Management (in press).