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VIEWPOINT

Tendon Pathology: Have we missed the first step in the development of pathology?

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End-stage tendon pathology is degenerative (3), but there is considerable debate about how we transition from normal tendon to degenerative pathology. Many hypotheses about the drivers of pathology exist, including inflammation (5), direct mechanical tissue damage (4), and a cell driven tissue response (1). It is likely that all are present and interact at different stages of the transition. Establishing the order of events and primary drivers may help identify interventions to manipulate outcomes or prevent tendon pathology developing.

Highly loaded energy storing tendons, which stretch and recoil to act like a spring and provide a mechanical benefit in higher level activities, are prone to pathology. The current concept is that the stretch all occurs within the tendon fascicles, incorporating first crimp straightening and then fascicle extension under load (7). However, although fascicle extension undoubtedly does occur, recent data indicate that tendon stretch and recoil also involves significant slide or shearing in the connective tissue *between* the fascicles in the endotendon or interfascicular matrix (IFM) (11). In vitro studies have shown that the fascicles within energy storing tendons are significantly less extensible than the whole tendon and that the IFM between them is also less stiff and more elastic, facilitating sliding behavior. Furthermore, ultrasound imaging of the Achilles tendon during walking or other physiological movements has demonstrated differential strains across the cross-section of the tendon, with deep regions of the tendon moving relative to superficial regions (8). Of further interest, the capacity for fascicle sliding has been shown to significantly reduce with aging both in vivo and in vitro, corresponding to an increase in injury risk (8, 13).

These data indicating that sliding of fascicles occurs during normal tendon loading thus imply less load through the individual tendon fascicles. As such, the intrafascicular tenocytes (hereon referred to simply as tenocytes) that have previously been proposed to drive tendon pathology may actually be protected from much of the high load stimulus that appears to initiate pathology, whereas cells in the IFM (IFM cells) are subjected to large strains, potentially incorporating tension, shear, and compression.

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What Do these New Concepts Mean for the Initiation and Progression of Tendon Pathology?

If sliding between fascicles and regions of a tendon facilitates physiological loading, then repetitive cyclic loading of tendon will result in continual interfascicular matrix shearing, potentially generating local damage in the IFM rather than the tendon fascicles. This in turn may initiate a reactive response in these interfascicular cells. Homeostatic maintenance of tendon requires the fine balance of use and repair, and if this is lost in the IFM region, breakdown of the IFM will result, exposing the fascicles and the tenocytes to loads they were previously protected from (Fig. 1). This in turn could result in a response in the tenocytes and further deterioration of the both the IFM (that is absent in tendon pathology) and the tendon fascicles. Initial tendon injury may thus center on the IFM, not the fascicles.

Tissue and clinical correlates. The IFM is less dense and organized than fascicular tissue and is continuous throughout the tendon and with the peritendon structures. The IFM of energy storing tendons has been shown to be proteoglycan and elastin rich, ideal for facilitating sliding and recoil (2, 11, 12). The IFM has more cells than found in fascicles, with intriguing evidence that those cells are also more responsive to altered loading conditions. IFM cells show significantly greater changes in cilia length under stress deprivation conditions than seen in fascicular cells (6) and also a more rapid and more pronounced response to a loading insult (9). Furthermore, the turnover or renewal rate of IFM is an order of magnitude faster than seen in fascicles (12), allowing for a continual process of mechanically initiated cell driven repair in the IFM.

Positional tendons (non-energy storing tendons), in which pathology is rarely reported clinically, are less reliant on fascicle sliding and have more fascicle lengthening to manage applied loads (11). This suggests there is less risk of IFM damage during use, and this, alongside the lower loads experienced by these tendons, may make them less vulnerable to developing pathology.

It is of particular note that older tendons that are vulnerable to tendon pathology have age-related changes in tendon properties only in the IFM (13), where stiffening reduces the efficiency of fascicle sliding and increases the risk of IFM damage during tendon use, correlating with a reduction in nonuniform loading across the tendon during use (8).

Taken together, a reactive, mechanoresponsive IFM cell phenotype may be important to facilitate healthy maintenance

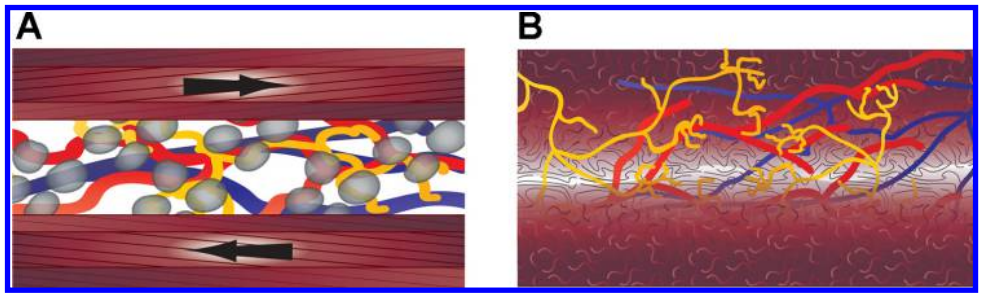

Fig. 1. Intact interfascicular matrix (*left*) and the loss of the interfascicular matrix (*right*), exposing the intrafascicular tendon cells to load and by-products from overload not previously experienced.

of the IFM. However, the potential for IFM damage during loading, in conjunction with the reactive phenotype of IFM cells, may explain the predisposition to IFM breakdown and eventual fascicular tendon pathology.

These concepts fit with the continuum model of tendon pathology (1), where the reactive stage on ultrasound imaging is consistent with intact fascicles and swelling in the IFM, which likely results from an increase in proteoglycans and adjuvant water. It likely also explains the reversibility of reactive tendon pathology because the fascicles remain intact. By contrast, chronic degenerative tendon pathology has little or no IFM, suggesting substantial catabolic activity (10). Degenerative pathology is hypercellular in nature (3); it has always been unclear where the additional cells come from, and they may be the cells originally in the IFM.

Where to from Here?

So how may we investigate this further? Ultrasound imaging is sensitive to a fascicle level, so changes in the IFM might be interpreted as a reactive tendon in the continuum model. Furthermore fascicle-level image resolution provides the potential to use ultrasound to measure and monitor fascicle sliding to determine healthy IFM function. Newer MR imaging techniques that can image proteoglycans may also be helpful in delineating where the first changes occur in the tendon after overload.

Further basic science studies must focus on IFM cell mechanobiology and link in vivo and in vitro IFM mechanics to explore this hypothesis. Identifying the early pathophysiology of tendinopathy offers exciting opportunities. There is potential for both pharmacological interventions and optimum exercise based treatments with a better understanding of IFM mechanics.

Clinically, as this hypothesis fits nicely in the reactive phase of the continuum model (1), it would indicate that early management should aim to reduce energy storage loads. A reduction in energy storing loads would allow more time for the proteoglycan content of the IFM to facilitate sliding without risking damage to the IFM or fascicles and reducing impact on the cell environment. In addition, activities such as isometrics, where heavy loads are placed on the tendon without associated movement, will likely minimize IFM sliding while still maintaining use of the muscle-tendon complex. Further clinical, mechanical, and biological evidence to provide evidence for this theory are required.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

J.L.C. and H.R.S. drafted manuscript; J.L.C. and H.R.S. edited and revised manuscript; J.L.C. and H.R.S. approved final version of manuscript.

REFERENCES

1. **Cook JL, Purdam CR.** Is tendon pathology a continuum? A pathology model to explain the clinical presentation of load-induced tendinopathy. *Br J Sports Med* 43: 409–416, 2009. doi:10.1136/bjsm.2008.051193.
2. **Godinho MSC, Thorpe CT, Greenwald SE, Screen HRC.** Elastin is localised to the interfascicular matrix of energy storing tendons and becomes increasingly disorganised with ageing. *Sci Rep* 7: 9713, 2017. doi:10.1038/s41598-017-09995-4.
3. **Khan KM, Cook JL, Bonar F, Harcourt P, Astrom M.** Histopathology of common tendinopathies. Update and implications for clinical management. *Sports Med* 27: 393–408, 1999. doi:10.2165/00007256-199927060-00004.
4. **Kjaer M, Langberg H, Heinemeier K, Bayer ML, Hansen M, Holm L, Doessing S, Kongsgaard M, Krogsgaard MR, Magnusson SP.** From mechanical loading to collagen synthesis, structural changes and function in human tendon. *Scand J Med Sci Sports* 19: 500–510, 2009. doi:10.1111/j.1600-0838.2009.00986.x.
5. **Rees JD, Stride M, Scott A.** Tendons–time to revisit inflammation. *Br J Sports Med* 48: 1553–1557, 2014. doi:10.1136/bjsports-2013-092459.9.
6. **Rowson D, Knight MM, Screen HRC.** Zonal variation in primary cilia elongation correlates with localized biomechanical degradation in stress deprived tendon. *J Orthop Res* 34: 2146–2153, 2016. doi:10.1002/jor.23229.
7. **Screen HRC, Lee DA, Bader DL, Shelton JC.** An investigation into the effects of the hierarchical structure of tendon fascicles on micromechanical properties. *Proc Inst Mech Eng H* 218: 109–119, 2004. doi:10.1243/095441104322984004.
8. **Slane LC, Thelen DG.** Achilles tendon displacement patterns during passive stretch and eccentric loading are altered in middle-aged adults. *Med Eng Phys* 37: 712–716, 2015. doi:10.1016/j.medengphy.2015.04.004.
9. **Spiesz EM, Thorpe CT, Chaudhry S, Riley GP, Birch HL, Clegg PD, Screen HRC.** Tendon extracellular matrix damage, degradation and inflammation in response to in vitro overload exercise. *J Orthop Res* 33: 889–897, 2015. doi:10.1002/jor.22879.
10. **Streit JJ, Shishani Y, Rodgers M, Gobezie R.** Tendinopathy of the long head of the biceps tendon: histopathologic analysis of the extra-articular biceps tendon and tenosynovium. *Open Access J Sports Med* 6: 63–70, 2015.
11. **Thorpe CT, Godinho MSC, Riley GP, Birch HL, Clegg PD, Screen HRC.** The interfascicular matrix enables fascicle sliding and recovery in tendon, and behaves more elastically in energy storing tendons. *J Mech Behav Biomed Mater* 52: 85–94, 2015. doi:10.1016/j.jmbbm.2015.04.009.
12. **Thorpe CT, Peffers MJ, Simpson D, Halliwell E, Screen HRC, Clegg PD.** Anatomical heterogeneity of tendon: Fascicular and interfascicular tendon compartments have distinct proteomic composition. *Sci Rep* 6: 20455, 2016. doi:10.1038/srep20455.
13. **Thorpe CT, Udeze CP, Birch HL, Clegg PD, Screen HR.** Capacity for sliding between tendon fascicles decreases with ageing in injury prone equine tendons: a possible mechanism for age-related tendinopathy? *Eur Cell Mater* 25: 48–60, 2013. doi:10.22203/eCM.v025a04.