Basic Science and Pathophysiology of Tendons

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ABSTRACT

This monograph summarizes the basic clinical science and anatomy of healthy tendons. It describes typical changes in tendons as we age and discusses the influence of exercise and sex hormones on tendon function. Clinical assessment of tendon function is then discussed, followed by a description of the etiology of primary and secondary tendinopathies. Vicenzino and Coombes' integrated model of lateral epicondyle tendinopathy is used as a paradigm to understand the impairments associated with tendinopathies throughout the body, highlighting similarities and variations at different sites of injury. Overarching principles of diagnosis are provided. The monograph concludes with an overview of treatment principles, and presents 3 case studies to demonstrate application of these principles to clinical reasoning.

Key Words: connective tissue, injury, mechanotherapy, overuse

LEARNING OBJECTIVES

Upon completion of this monograph, the course registrant will be able to:

1. Understand the anatomic and regional variation in structure and function of normal tendons, including the types of loads they experience during typical movements.
2. Understand the impact on tendon function of exercise, aging, hormones, medical conditions, and medications.
3. Describe the pathophysiology of primary and secondary tendinopathy.
4. Develop an assessment plan for tendon tissue changes and alterations in the motor and pain systems associated with tendinopathy.
5. Conduct an evidence-based differential diagnosis of tendinopathy and describe situations when a tissue-based diagnosis may not be feasible or necessary.
6. Explain the range of prognoses for tendinopathies and clinical features that may influence outcomes.
7. Apply principles of evidence-based management to develop a treatment plan for tendinopathy.

INTRODUCTION

Many tendinopathies that occur in the general population are mild, transient episodes that resolve spontaneously without much treatment.[1] However, the "problem tendons" that are associated with persistent pain can test the patience and experience of even the best therapists. Persistent tendinopathies make up a substantial portion of many physical therapists' caseloads. The recovery time for most of these recalcitrant cases typically is measured in months rather than weeks. Some tendinopathies fail to completely resolve despite optimal rehabilitation, resulting in ongoing psychological impact on the patient and frustration for the therapist.

Tendinopathy may be thought of broadly in 2 categories: primary tendinopathy (no known medical cause) and secondary tendinopathy (associated with a medical condition such as high cholesterol, diabetes, an inflammatory condition, or ingestion of certain medications). Primary tendinopathy in healthy adults may be further subdivided into those with a clear mechanical cause, or those with no clear cause other than the presumed effects of age or gradual wear and tear. Patients may present after a short duration of symptoms (<4 weeks; acute), or more typically, with a history of long-standing complaints (months; chronic), including repeated episodes where the pain is exacerbated (acute on chronic). A challenge for therapists is that, unlike a straightforward acute injury such as a ligamentous sprain or muscle tear, the actual relationship between tissue pathophysiology and symptoms can be complex and may not be easy to determine for an individual patient.

This monograph reviews and critiques some pertinent basic science of tendons and tendon pathophysiology, including the basic science underpinning typical physical therapy treatment approaches. This knowledge will form a foundation for accompanying monographs on the assessment and treatment of specific tendinopathies and contribute to a base of knowledge for clinical reasoning and problem solving for tendinopathies throughout the body, particularly those for which clinical guidelines are not available.

NORMAL TENDON

In this section, the normal structure and function of tendons is reviewed. Clearly, an understanding of tendon anatomy and physiology is necessary when designing assessment and treatment strategies.

Anatomy

Tendon may be thought of as an organ made up of different types of tissue. These tissues work together to achieve 1 or more functions, depending on the anatomic location:

- Efficiently transmitting the force generated by a muscle across 1 or more joints to its insertion, thereby facilitating

movement with minimal delay between muscle activation and joint rotation
- Minimizing stress concentration at the myotendinous and osseotendinous junctions by maintaining an appropriate gradation of material properties
- Providing a pulley function to enhance the efficiency and design of the musculoskeletal system, eg, fibularis tendons, patellar tendon, carpal tendons
- Facilitating proprioception by transmitting external forces to the muscles and their Golgi tendon organs
- Absorbing and releasing energy to assist with locomotion or other cyclic activities, thereby improving the efficiency and energy cost of movement[2]

Macroscopically, normal tendon is a dense structure, appearing as glistening white due to its high Type I collagen content. The overall shape of tendons varies considerably. For many tendons, their structure is intimately related to the muscle from which they originate, with some muscles containing a long tendinous component that extends deep into the muscle belly, thereby increasing the strength of the muscle-tendon junction, the semitendinosus muscle being a prime example.

An amazing anatomic variation in the macroscopic organization of tendons reflects their distinctive functions at different joints. For example, consider the differences in structure and function of 3 different tendons: the Achilles, the patellar, and the supraspinatus.

The Achilles tendon, which is subjected to the highest loads of any tendon in the human body,[3] is composed of 3 sub-tendons arising from the 2 heads of the gastrocnemius and the soleus muscles that rotate as they descend in a spiral manner toward the calcaneal insertion.[4] This "internal" spiraling may improve the elasticity of the Achilles tendon,[4] an important property for an energy-storing tendon (see below), thereby minimizing the development of excessively high strain levels. Many individuals have a plantaris tendon that can insert into either the Achilles tendon itself or the calcaneus, and whose size varies considerably.[5] Although Achilles tendon loads are viewed as primarily tensile, the actual forces through the tendon are complex with varying amounts of tension, compression, and internal shearing.

Conversely, despite earlier speculation that the deep proximal region would experience compression, loading through the patellar tendon is mostly tensile.[6] Finite element modeling demonstrates that the predominant type of loading in the patellar tendon is tensile strain, and that the levels of tensile strain are greatest in the deep, proximal region of the patellar tendon corresponding to the most common location of pathology.[7] Unlike the Achilles, the patellar tendon directly joins 2 bony segments over a relatively short distance and does not demonstrate any degree of spiral. This lack of a spiraling structure may explain in part the observation that patellar tendons are subjected to significantly higher strains than the Achilles tendon during maximal voluntary efforts, frequently exceeding the suggested safety threshold of 9%.[8]

Finally, the supraspinatus tendon experiences a distinctive combination of tension, shear, and compression due to its contacts with the head of the humerus and the acromion, its interdigitation with collagen fibers from the infraspinatus tendon, and its large working range of motion.[9] The compressive loads through the rotator cuff tendon may be increased substantially if the subacromial bursa is enlarged, as is seen after injury, or if the subacromial space is narrowed by hypertrophy of the acromioclavicular joint.[10]

It is clear from the above considerations that each tendon displays region-specific anatomy leading to specific structure-function relationships that must be considered during assessment and rehabilitation.

Tissue and Cellular Components

Tissues are composed of cells, extracellular matrix, and water.[11] The major tissue type in tendon is known as **dense connective tissue**. This type of tissue is characterized by a high content of well-organized **Type I collagen**, a smaller amount of Type III and V collagen, as well as non-collagenous molecules, water (associated with glycosaminoglycans, as in cartilage), and fibroblasts. The dense connective tissue is the *load-bearing* component of tendon. The majority of tendon fibroblasts residing within this dense connective tissue zone are **tenocytes**, which are identified by their location within the load-bearing region and their high expression of scleraxis, a gene that controls collagen synthesis.[12] A distinguishing feature of many tendons is the presence of a longitudinal *crimp* pattern, which is generated by the constant, gentle tugging of the tendon cells on the collagen, causing it to slightly buckle in a regular wave-like pattern.[13]

Regions of dense connective tissue are surrounded by, and may be internally demarcated by, areas of **loose connective tissue**.[11] Loose connective tissue is a meshwork of more irregularly organized Type III collagen and fibronectin. This tissue compartment contains sensory nerves, blood vessels, adipocytes, and immune cells such as macrophages, mast cells, and lymphocytes. Areas of loose connective tissue are anatomically diverse and have been given a variety of labels that are sometimes used inconsistently.[14] Endotenon and interfascicular matrix refer to the same structure, consisting of seams of loose connective tissues that run generally along the longitudinal axis of the tendon. According to the classic histological description by Pekka Kannus,[15] some tendons are surrounded by a "fine connective tissue sheath called epitenon" that is surrounded by an outer loose connective tissue layer known as paratenon. The epitenon consists of a *closed duct* lined by a visceral and parietal layer of synoviocytes that produce *peritendinous fluid* (synovial fluid). Benjamin et al[14] observed that these histological terms have not been used consistently and suggest that the term *paratenon* be applied to the tendon sheath,

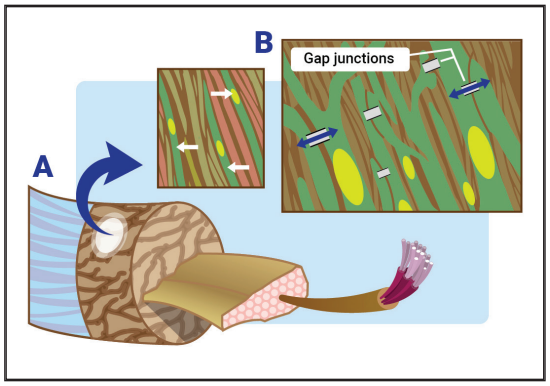
ie, Kannus' *epitenon*. However, this suggestion appears not to have been generally adopted. Contemporary imaging reports frequently refer to the paratenon of the Achilles, which is not a fully sheathed tendon. Some authors refer to the combination of the sheath (epitenon) and its surrounding loose connective tissue (paratenon) as the peritenon.[16,17] Finally, a subpopulation of loose connective tissue fibroblasts within or surrounding the tendon are pluripotent, ie, they can differentiate into various cell types, such as cartilage, fat, bone, or tendon.[18]

Tenocytes within the load-bearing part of a tendon are distributed among the collagen fibers in a highly inter-connected network linked by cellular extensions (**Figure 1**).[19] This network arrangement allows tenocytes to communicate with one another when they experience a mechanical perturbation such as a tensile force. Communication through **gap junctions** amplifies and sensitizes the tendon's ability to monitor and adapt to changing levels of load. Tenocytes, through processes that are still somewhat mysterious, are able to sense both the magnitude and direction of applied force; they respond to this information by orienting themselves longitudinally along the force vector.[20] This process ensures that the tissue is organized to withstand the applied loads appropriately, consistent with Wolff's law of bone remodeling.[21] During periods of intense loading, tenocytes can detach themselves temporarily from the matrix and retract their extensions, assuming a more rounded appearance, which likely protects them from damage, ie, reduces the amount of strain they experience.[22] Tenocytes are characterized by several force-sensing apparatus, including stretch-activated ion channels and **integrins**.[23] Integrins are cell surface receptors that connect the tenocyte's internal cytoskeleton to the surrounding collagen fibers or to other components of the extracellular matrix such as fibrin or fibronectin that are present in large quantities after acute or chronic injury.[24] The tenocytes respond to the sensation of tensile load across the integrins by activating cell signaling pathways including mTOR, which results in enhanced collagen synthesis.[23] This cell signaling mechanism is suspected to underpin the ability of exercise to promote repair of injured tissue (**mechanotherapy**).[25]

Tenocytes regularly subjected to compression or shear loading demonstrate a more chondrocyte-like morphology and produce a more cartilage-like matrix.[26] This change in phenotype is presumed to be an adaptation that protects the tissue from compressive damage. Whether tenocytes differentiate into chondrocytes or whether a local population of pluripotent cells is responsible for this adaptation is not yet known, but tendon appears remarkably plastic in that a chondrocyte phenotype can appear when compression is applied and disappear if compression is removed. Prominent areas of chondrocyte metaplasia at the tendon insertion could also indicate an adaptive response, ie, the reinforcement of the tendon's fibrocartilage insertion region in response to heavy loading.

Tenocytes are highly load-dependent for survival. If the tension in the tendon is released, for example, after an acute tendon rupture, the cells become catabolic, rapidly digesting collagen through the action of matrix metalloproteinases and reducing their population numbers through a process of cell death known as apoptosis.[27] This process probably underpins some of the focal degeneration and thinning seen in larger areas of tendon disruption; it may also occur on a microscopic scale if microregions of tendon experience a loss of mechanical integrity leading to loss of tension. The ability of tissue to restore homeostasis and prevent degeneration from loss of mechanical loading might depend on whether the micro-ruptured region can heal, ie, be cross-linked back into the load-bearing force vector.

Figure 1. Healthy Tendon Architecture[a]



A, Healthy tendon is a dense, glistening white tissue with great strength and elasticity. The hierarchic structure is illustrated including tendon fibrils associating to form a fiber, and bundles of fibers forming a fascicle surrounded by looser connective tissue. Inset: a tenocyte (green) is shown surrounded by the rope-like collagen fibers, each made up of many fibrils. B, The collagen fibers have been removed to illustrate the interconnected network of tenocytes.

[a]Adapted from Egerbacher M. Arnoczky SP, Caballero O, Lavagnino M, Gardner KL.[27] Figure based on concept art by Vicky Earle. Illustration by Kinstler Design.

Collagen Synthesis

The synthesis and organization of collagen is a multi-stage process,[28] beginning with the translation of mRNA into immature collagen proteins inside the tenocyte, the assembly of 3 of these proteins into a triple-helix formation, secretion and further processing of these procollagen units, association of these secreted units into **fibrils**, and finally, accretion of fibrils into **fibers**. Tenocytes are thought to regulate the size of fibrils by adjusting the levels of regulatory proteins such as decorin, or the relative amounts of Type I, III, and V collagen that are

incorporated into each fibril. Tenocytes also secrete a powerful enzyme into the extracellular space, **lysyl oxidase**. Lysyl oxidase converts collagen fibrils into a mature form by creating internal, trivalent cross-links, thereby improving the fibril's load capacity.[28] Lysyl oxidase is well positioned as an adaptive mechanism to adjust the stiffness of tendon tissue by altering the level of cross-linking inside the fibrils.

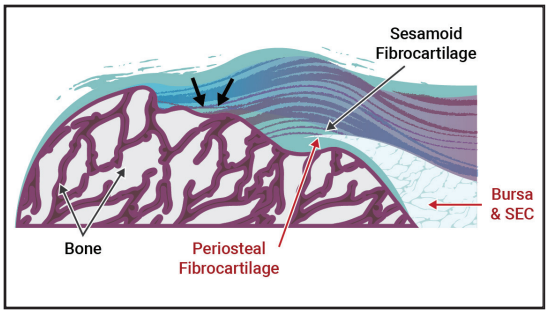
Tissue Biomechanics

Ultimately, the toughness of the tendon (defined as the area under the slope of its load-deformation curve, ie, stiffness) depends on the number of intact collagen fibers that can transmit force from one end of the tendon to the other, and the amount of cross-linking within and among collagen fibrils. Please note that the use of tendon stiffness in this biomechanical (scientific) context is not the same as the use of the word stiffness by physical therapists or their patients to describe a symptom or sensation, eg, morning stiffness. The word stiffness in the former scenario refers to biomechanical properties and in the latter to sensory experiences.

One study using electron microscopy has shown that the majority of collagen fibers in a healthy tendon run from the muscle all the way to the bone, but that some fibers may fuse with others before they reach the bone.[29] There is likely great anatomic variety in the nature and number of internal collagen fiber attachments and fusions. This phenomenon is far more difficult to study compared to muscle fascicles, which can be visualized with ultrasound; individual collagen fibers can only be visualized in tissue biopsies under a microscope, making it impossible to trace the transmission of force along the tendon at the fiber level. At a slightly larger scale, new techniques such as ultrasound speckle tracking reveal some interesting insights into force transmission within tendons.[30] For example, during isometric exercise, the Achilles tendon experiences greater displacement in the deep anterior third of the tendon than in the superficial posterior region.[30] This type of research eventually may be useful for therapists who want to ensure that the exercise they are applying is targeting the region of interest.

As tendons approach the osseotendinous junction, their toughness (stiffness) increases.[31] This is likely an adaptive mechanism that prevents an abrupt transition between soft and hard tissues, thereby minimizing stress concentration. The osseotendinous junction is worth special attention, as many tendinopathies are focused at this location and may involve not only the tendon, but also the fibrocartilage insertion and bone. This area can also be considered an entity unto itself – the **enthesis organ** (**Figure 2**). The enthesis organ is composed of the following tissues: fibrocartilage, bone, bursae, and adipose. All these tissues are well-vascularized compared to the load-bearing regions of the tendon. If the enthesis organ is irritable, extreme joint angles such as full dorsiflexion of the ankle for the Achilles tendon or adduction of the hip for the gluteal tendons should be used cautiously, as they may be compressing

Figure 2. The Tendon Enthesis Organ[a]



Note the position of the bursa, between the tendon and the bone/fibrocartilage. Any of these tissues can become a source of nociception with overuse or injury.

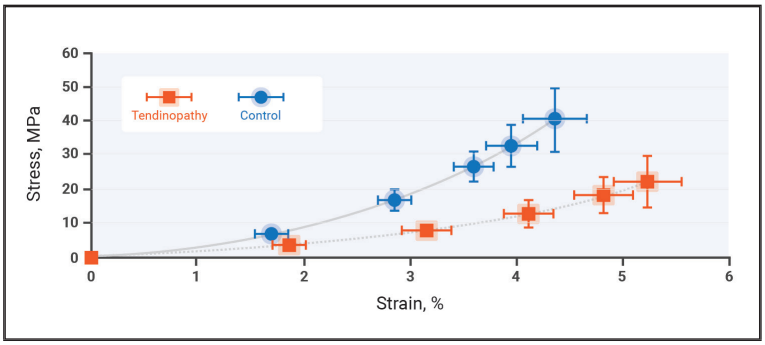
Abbreviation: SEC, synovioentheseal complex

[a]Adapted from McNeilly CM, Banes AJ, Benjamin M, Ralphs JR.[19] Illustration by Kinstler Design.

an irritable bursa between the tendon fibrocartilage and the adjacent bone.[32]

An important characteristic of tendon tissue biomechanics is demonstrated by the stress-strain (or load-deformation) curve (**Figure 3**).[33] As load is placed on the tendon, initially there is relatively large tendon elongation as collagen fibers unkink and uncrimp. The linear portion of the stress-strain curve is characterized by elongation of collagen fibrils, which resist being deformed but undergo a gradually increasing amount of strain as the load is increased. The amount of energy the tendon can ultimately absorb is represented by the area under the load deformation curve. If the applied load continues to increase, eventually the collagen fibrils and fibers will begin to fail, with a resultant loss of the tendon's overall stiffness and load capacity. The maximum stress the tendon can endure prior to failure (rupture) is known as the ultimate tensile strength. Repeated, sub-failure loading of the tendon can lead to microscopic injury to fibrils and fibers.[34] This microscopic injury is characterized by the appearance of features such as kinks as the tightly packed fibrils lose integrity.[34] It has not been possible to demonstrate this process in humans, due to the same issues of visualization discussed above as well as ethical constraints. However, there is no reason to think that humans would somehow be immune to the phenomenon of sub-failure injury if their tendons were stretched beyond their yield point (the point on the load-deformation curve where collagen fibers begin to fail, which leads to a loss of mechanical properties of the tissue). In fact, micro-ruptures do not even show up on standard histological preparations; electron microscopy is necessary to visualize

Figure 3. Stress-strain Curve[a]



Currently a laboratory-based technique, the slope of the line which results from plotting stress (load) and strain (deformation) is the stiffness or modulus of the tissue. The tendinopathy curve illustrates the tissue impairment (reduced tendon stiffness) many people likely present with, as a result of inferior tendon tissue quality (eg, disorganized and smaller collagen fibrils, increased water content).

[a]Adapted from Ayra S, Kulig K.[33] Illustration by Kinstler Design.

them.[17] Kink bands, which appear after repeated sub-failure loading in a laboratory, are a prominent feature in human tendinopathy biopsies observed under a transmission electron microscope.[35]

Biomechanical models indicate that tendons subjected to high loads are regularly stretched beyond their yield point, which means that ongoing collagen synthesis activity is required to maintain tendon stiffness.[36] Tendon radioactivity data suggest that human tendons do not incorporate new collagen beyond adulthood[37] but the sensitivity of the Carbon 14 technique to detect minor ongoing repairs to the tendon matrix is not known.

Despite the importance of tendon toughness (stiffness) as a key indicator of tendon function, it still is unknown whether there is an optimal level of tendon stiffness for a given tendon. In fact, accurate estimates of normal tendon stiffness are not available for different demographic groups, let alone for individuals with different types or stages of injury. Conceptually, stiffness is important because one knows it tends to be lower in injured or tendinopathic tendons, and it decreases with age. Exercise to improve tendon stiffness may be a reasonable goal in some situations such as after injury or in an aging athlete, and efforts are currently underway to allow clinicians to routinely measure this parameter.

Tendons also exhibit viscoelasticity, that is, time-dependent behavior related to the presence and displacement of water between the collagen fibers. The slower the loading rate, the less force is required to achieve the same tendon elongation.[38] Creep refers to the gradual lengthening of a tendon after prolonged static or cyclic loading. After a 5K (3-mile) run, the Achilles tendon is significantly longer, but by only an average of 1 mm.[39] This may be due to either displacement of water from the tendon, or a slight increase in flexibility as the tendon tissue warms up.

Blood Supply

The tendon blood and lymph supply are housed in the loose connective tissue layers.[15,40] Tendon blood flow is regulated dynamically by dilation or constriction of vascular smooth muscle, with blood flow increasing significantly after exercise or injury. There is no indication that a healthy tendon's blood flow is insufficient to meet the healthy tendon's metabolic demand. Following injury, the tendon lesion is expected to be hypoxic, resulting in upregulation of angiogenic factors like VEGF-A to stimulate the blood vessel formation required for healing. Older theories that the Achilles tendon had a "watershed" area of reduced vascularity have been disproven with more sensitive measurement techniques,[41] although the rotator cuff does demonstrate a well-known hypovascular zone close to its humeral insertion.[42] On the whole, tendons are relatively hypovascular compared to faster-healing tissues like skin or muscle and thus take a longer time to heal following injury.

Tendon Adaptation to Exercise

The concept that tendons can adapt to exercise is a relatively new one. Tendons regularly subjected to loading, such as the Achilles tendons of marathon runners or the dominant leg's patellar tendon in athletes who lunge repeatedly (eg, fencers), are significantly hypertrophied.[43] However, the amount of hypertrophy typically is small compared to the magnitude of related muscle hypertrophy (mm rather than cm). Because tendon hypertrophy is on the scale of millimeters, it cannot be measured routinely in the clinic. Nevertheless, it does happen, and making tendons thicker can be a reasonable goal for injury prevention. If all other things are held constant, a thicker tendon will be stiffer and stronger. (This is not to be confused to pathological tendon thickening, discussed below, where the thickening is composed of inferior scar-like, hypervascular tissue with higher water content).

Most of the studies that have looked at tendon adaptation before and after an exercise intervention have used resistance training. However, as pointed out above, runners do display thicker tendons than non-runners.[43] In a cross-sectional study, looking at tendon stiffness in 3 cohorts of runners (5K, 10K, or half marathon), the average tendon stiffness was found to increase with the distance being run (which presumably reflected