[Athletic Training]

CEU

The Mature Athlete: Aging Tendon and Ligament

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Context: Aging changes the biology, healing capacity, and biomechanical function of tendons and ligaments and results in common clinical pathologies that present to orthopedic surgeons, primary care physicians, physical therapists, and athletic trainers. A better understanding of the age-related changes in these connective tissues will allow better patient care.

Evidence Acquisition: The PubMed database was searched in December 2012 for English-language articles pertaining to age-related changes in tendons and ligaments.

Level of Evidence: Level 5.

Results: The mature athlete faces challenges associated with age-dependent changes in the rotator cuff, Achilles tendon, lateral humeral epicondylar tendons, quadriceps tendon, and patellar tendon. The anterior cruciate ligament and the medial collateral ligament are the most studied intra-articular and extra-articular ligaments, and both are associated with age-dependent changes.

Conclusion: Tendons and ligaments are highly arranged connective tissue structures that maintain joint motion and joint stability. These structures are subject to vascular and compositional changes with increasing age that alter their mechano-transduction, biology, healing capacity, and biomechanical function. Emerging research into the etiology of age-dependent changes will provide further information to help combat the age-related clinical complications associated with the injuries that occur to tendons and ligaments.

Keywords: tendon; ligament; age-related; biomechanics; rotator cuff; Achilles tendon; ACL

TENDON

Tendon Structure

Tendons are dense, regularly arranged connective tissues that attach muscle to bone and produce joint motion by transferring force from muscle to bone. Tendons are composed primarily of type I collagen arranged in parallel fibrils with the remaining 20% to 30% of dry weight composed of proteoglycans, glycosaminoglycans, other collagens (type III, V, XII, and others), and elastin.[61,108,118] These minor constituents, such as type V collagen and decorin, help regulate fibrillogenesis.[20,86,114,115] Tendon structure is highly regular with collagen forming triple helices (approximately 300 nm in length and 1.5 nm in diameter), which pack together to form microfibrils,[45] which interdigitate to form fibrils (50 to 200 nm in diameter), which coalesce to form fibers (3 to 7 µm in diameter), which combine to form fascicles, which are bundled together to form a tendon (mm or cm in diameter).[57] The mechanical properties of tendon come from its highly oriented structure. It is able to resist tensile stress in the direction of its fiber orientation because of the collagen structure and it is able to resist some compressive stress because of its proteoglycan content.

Tendons have different mechanical properties dependent on anatomic location, exercise, immobilization, and age of the tendon. Material and structural properties of the tendon increase from birth through maturity and then decrease from maturity through old age. Tendon injuries correlate positively with patient age, but the cellular changes in the tendon associated with age are somewhat less clear. Some of the more commonly studied tendons are rotator cuff, Achilles, lateral humeral epicondylar, quadriceps, and patellar tendons because as people age, these areas become clinically problematic.

Vascular Supply

Tendons are metabolically active and are provided with a rich vascular supply during development.[82] Tendons do not undergo neovascularization under normal circumstances, but during pathologic processes, changes in vascularity may take place. Tendons receive vascular supply through the musculotendinous junction, the osseotendinous junction, and

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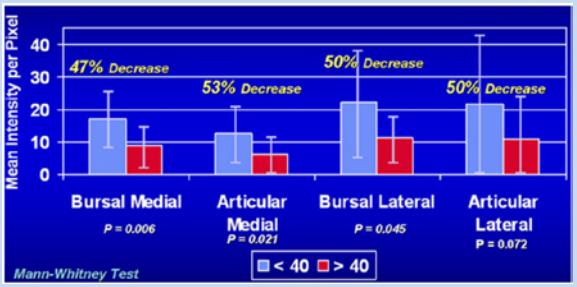

Figure 1. Intratendinous vascularity by age. Comparative analysis of intratendinous supraspinatus vascularity in patients younger than and older than 40 years old. Error bars show the standard deviation. Reprinted with permission from Rudzki et al.[93]

the vessels from the various surrounding tissues including the paratenon, mesotenon, and vincula.[2,24,27,102] Tendons in different areas of the body receive different amounts of blood supply. The vascular supply of the specific tendon also relates to whether or not it is a sheathed tendon. If the tendon is sheathed, such as the digital flexor tendons, it receives blood supply from the mesotenon, vincula, and diffusion from vascularized surrounding segments. Tendons that are not sheathed are covered with a paratenon and have the advantage of a local extrinsic vascular supply with branches forming an intratendinous vascular network with multiple anastamoses. Tendon vascularity can be compromised at junctional zones and at sites of friction, torsion, or compression.

The vascular supply to the rotator cuff tendons is a 6-artery supply.[27] However, it is not uniform to each tendon, with the supraspinatus having relatively reduced vascularity.[85] The region of relative avascularity in the supraspinatus, called "Codman's critical zone," was described by Codman and Akerson in 1931.[32] This area is actually hypovascular as the vascularity increases when the compression applied by the humeral head is removed.[69]

In addition to the supraspinatus having reduced tendon vascularity, the biceps,[85] Achilles,[95,99] patella,[31] and posterior tibial tendon[37] have areas of reduced vascularity. The Achilles tendon receives blood supply from the musculotendinous junction, the osseotendinous junction, and the paratenon, with the posterior tibial artery supplying the major contribution. However, histological analyses proved that the Achilles tendon has a poor vascular supply through its length, as shown by the low number of blood vessels per cross-sectional area.[2] The Achilles tendon has a hypovascular zone approximately 2 to 7 cm proximal to its bony insertion, with this area at the highest risk of rupture and surgical complications.[29]

Biology of Tendon Aging

Healthy tendon relies on a normal vascular supply and efficient mechanotransduction with cells that are capable of responding to mechanical cues with biochemical signals to maintain tendon development, homeostasis, healing, and degeneration.[12,111]

Changes in Vascular Supply

Astrom and Rausing[14] noted that patients with Achilles tendinopathy demonstrated hypervascularity of the tendon with unevenly distributed thick-walled vessels as compared with healthy controls. A recent ultrasound study evaluating the volume of neovascularity in tendinopathic Achilles tendons revealed that 97.3% of the tendons had evidence of neovascularization and 55.6% of the tendons had neovascularization at the location of the tendon thickening.[122]

The origin of rotator cuff disease is controversial, with tendon ischemia, extrinsic compression, and chronic repetitive microtrauma having been cited as factors. There are both extrinsic as well as intrinsic reasons for tendon failure and age-related degeneration. A recent in vivo study evaluating the vascularity of rotator cuff tears using ultrasound showed that there was a significant decrease in blood flow in the intratendinous region in elderly subjects compared with younger subjects but no differences in the bursal blood flow suggesting an age-related decrease in intratendinous vascularity.[39] Rudzki et al[93] corroborated those results by finding a significant decrease in blood flow in the supraspinatus tendon in patients older than age 40 years compared with younger patients after exercise (Figure 1). Several studies have hypothesized that tendon vascularity is compromised at the articular surface of the distal aspect of the supraspinatus tendon.[25,70,85,92] Adler et al[1] reported an in vivo ultrasound study demonstrating a consistent region of decreased vascularity at the articular medial margin of the rotator cuff with significantly less flow compared with the bursal side. This study also suggested a trend toward decreased blood flow with increasing patient age.[1]

Vascular changes also play a role in the pathogenesis of patellar tendinitis. In a study of chronic patellar tendinitis, there was capillary proliferation and prominent angiogenesis in the degenerated region of tendon.[58,124] The paratenon surrounding the patellar tendon can also be a site of chronic pain with marked neovascularization and degenerative vascular changes,[16,63] with hypervascular changes resulting in abnormal blood flow and ischemic pain during exercise.[63] An ultrasound study on the neovascularization of the patellar tendon in symptomatic elite athletes with patellar tendinitis noted that 60% had neovascularization.[47] A recent study on patellar and Achilles tendons of elite badminton players showed that intratendinous vascularity tended to increase with strenuous activity, but it was only significantly increased in the dominant leg after repetitive loading.[21]

Bales et al[17] performed a microvascular anatomic study on the lateral epicondyle of the humerus and found 2 hypovascular zones. The first was at the proximal lateral epicondyle just distal to the supracondylar ridge and the second was distal to the lateral epicondyle on the deep surface of the common extensor tendon. The presence of these

hypovascular zones may preclude the normal inflammatory cascade and healing response to microtearing in this region of tendon.[17] Thus the common sites of clinical tendon degeneration with age show significantly altered tendon vascularity occurs with age and activity.

Changes in Mechanobiologic Environment

Tendon tissue homeostasis is based on the ability of the tendon cells to sense and respond to mechanical load through mechanotransduction.[19,48,94,113] The exact level of mechanical and biological stimulation required to maintain normal tendon homeostasis is not currently known, but it is widely believed that an abnormal level of stimulation (underload or overload) may play a role in the pathogenesis of tendinopathy.[8,10,52] Archambault et al[6] proposed an algorithm for the onset of overuse tendinopathy in response to repetitive loading. Repetitive strains below injury threshold resulted in degenerative changes in the tendon-matrix composition and organization, which led to transient weakness of the tissue making it more susceptible to continued load. Over time, the damage continued until tendinopathy developed.[6] Cyclic strain is beneficial to tendon health, but repetitive strain may result in overuse tendon injuries.[6,98]

Based on the theory that excessive loading of tendons during vigorous physical activity is the main stimulation for degeneration of the extracellular tendon matrix, several studies have looked at in vitro analyses of strain patterns and extrinsic factors that induce tendinopathy. Overstimulation in vitro of tendon cells increases inflammatory cytokines and degenerative enzymes.[4,5,18,19,105,112] The in situ environmental conditions in these studies are in a monolayer cell culture and may not replicate the 3-dimensional collagenous matrix found in vivo. In addition, the high strain magnitudes and durations may provide an artificially enhanced cellular response to the repetitive loading stimulus, suggesting that these in situ conditions may not be clinically relevant. Further study is necessary under clinical conditions to evaluate the theory of repetitive loading resulting in overuse.

An increase in the degradative enzyme production in aging tendons or tendons unable to maintain homeostasis has been postulated in several biochemical studies. Fu et al[38] showed that matrix metalloproteinase-1 (MMP-1) was increased in human patellar tendinosis tissue, and Riley et al[88] showed that MMP-1 levels were high in ruptured tendons compared with normal tendons. Tendinosis may result from increased MMP production as the pathology associated with tendinosis results in irregular orientation of collagen, fiber disruption, changes in fiber diameter, decrease in density of collagen, and an upregulation of collagen type III production.[50,53,55] The increase in MMP production has been associated with significant reductions in the tensile modulus and tensile strength of tendons.[65] In addition, MMP inhibitors have been shown in vitro to prevent the decrease in mechanical properties of stress-deprived tendons.[9]

In addition to the increase in MMP production, other studies have suggested a role for increased apoptosis in clinical cases of tendinopathy.[106,125,126] In degenerative supraspinatus tendons compared with normal controls, there was a significant increase in the number of apoptotic cells.[106,125] Egerbacher et al[33] reported an increase in the number of apoptotic cells in the stress-deprived rat tail tendon model.

Thus, as the tendon ages, it is subjected to more mechanical load and the sequela of that repetitive use may result in an increase in degradative enzymes, apoptosis, and resulting clinical tendinopathy or tendon rupture. Some authors, however, have proposed an alternative theory to tendon over-stimulation as the etiology of tendon degeneration. Arnoczky et al[7] proposed that understimulation may be a cause of tendinopathy as well. In tendons that have undergone an injury from a mechanical load, there are resulting damaged collagen fibers. These tendons are then understimulated because of the release of cellular tension on the remainder of that tendon structure. This understimulation may then induce apoptosis. Understimulation of tendon cells can produce a histological picture consistent with tendinopathy.[41] In an in situ rat tail tendon model, Arnoczky and colleagues showed that the alteration in cell-matrix interactions secondary to isolated tendon fibrillar damage could result in mechanobiological understimulation of tendon cells thereby resulting in an upregulation of collagenase mRNA expression and protein synthesis.[12,65-67] This results in an initial degeneration of the pericellular matrix, a decrease in the material properties of the tendon, risk of further damage or rupture with subsequent mechanical loading, and clinical and histological signs of tendinopathy eventually.

Alteration in Tenocyte Biochemistry and Failure of Healing Response

Ippolito et al[49] showed that with aging, rabbit tendon tissue extracellular matrix volume increases and the relative number of cells per unit of tendon decreases. The tenocytes also become longer and thinner and have decreased protein synthesis, and the collagen fibers become more disoriented with more variations in thickness due to an increase in collagen, a decrease in mucopolysaccharies, and a decrease in water content.[49] Riley et al[89] showed a significant decrease in total glycomaminoglycan, chondroitin sulphate, and dermatan sulphate with age in the supraspinatus tendon.

Tenocyte biology has been a particularly exciting topic of research for tendon healing and whether age has an effect on the ability of tenocytes to repair the surrounding tissue. Gerber et al[40] and Rodeo et al[90] demonstrated in animal studies that tendon to bone healing is a complex process that forms biomechanically inferior scar tissue rather than regenerated native tendon to bone attachments. Several studies on rotator cuff healing have noted that patient age is associated with increased healing complications.[22,78,97,121] Klatte-Schulz et al[60] showed that tenocyte-like cells from aged donors compared with younger donors showed a decreased cell growth and stem cell potential including potential for self-renewal and osteogenic differentiation, but no differences in cell density.

This suggests a slower metabolic rate for aged tenocyte-like cells and thus, possibly, a weaker tendon to bone healing response. Both aged and younger donor tenocyte-like cells can be stimulated with BMP-2 and BMP-7.[60] There is significantly increased cell activity, cell proliferation, and collagen type I synthesis following BMP-7 treatment in in vivo tendon studies.[104,120,123] Several in vivo studies have also shown improved tendon to bone healing and higher biomechanical strength following treatment with BMP-2 and BMP-7.[44,72,74,77,91] Importantly, Klatte-Schulz et al[60] showed no differences in decorin production based on age, which is an important factor given that decorin reduces scar formation and may improve the biomechanical properties of tendons.[51]

The histopathology associated with degeneration of rotator cuff tendons and lateral epicondyle tendons includes blood vessel wall changes, tenocyte loss, calcification, glycosaminoglycan infiltration, and fibrocartilaginous transformation.[28] These changes were variably and mildly present in younger patients (less than 39 years old) with only 17% of cadaveric tendons having these changes, but the abnormalities occurred in 40% to 50% of patients older than 40 years of age.[28]

Biomechanics of Tendon Aging

Tendon microarchitecture is disrupted with tendinopathy.[13,71] Specimens taken from torn tendons show disorientation of collagen fibers, thinning of the fibers, myxoid degeneration, chondroid metaplasia, calcification, and vascular infiltration.[43] Degeneration of tendons significantly reduces the tensile modulus and tensile strength of tendons.[65] However, it is unclear whether normal aging is always synonymous with changes in the biomechanical properties of tendons. Plate et al[83] demonstrated in rat Achilles tendons that the passive biomechanical properties of the muscle-tendon unit were altered by normal aging with a decreased relaxation response and increased stiffness in the middle-aged tendons as compared with the younger tendons.

Aging is associated with a decrease in muscle mass and muscle fiber cross-sectional area, which in combination with the structural changes in tendon aging such as collagen disorganization and decreased collagen content, can alter the biomechanical response of tendon tissue.[87] The current literature is not consistent, however, with Kubo et al[62] showing decreased Achilles tendon strain in older compared with younger patients, Onambele et al[81] showing increased strain, and Karamanidis and Arampatzis[56] showing no strain differences. Mouse tibialis anterior tendon modulus increased with age but was independent of changes in collagen fibril morphology or force-generating capacity of muscle.[119] Zhou et al[128] further showed that tendon self-renewal and differentiation capacity decreased with age by showing that progenitor stem cells, while present in both the young and old tendons, are reduced by 70% in stem cell number, have a lower cell proliferation, and have delayed cell cycle progression in older tendons.

Clinical Implications

Tendinopathy is a common clinical problem in patients, particularly with increasing age. The most common clinical tendon problems for the aging population are in the rotator cuff, Achilles, lateral elbow epicondyle, quadriceps, and patellar tendon. Yamaguchi et al[121] found in his landmark ultrasound study on symptomatic and asymptomatic rotator cuff tears that there was a high correlation between the onset of rotator cuff tears (either partial or full thickness) and increasing age. In a group of patients with shoulder pain evaluated prior to surgical intervention, patients age 65 years and older had a full-thickness rotator cuff tear prevalence of 22%.[34] In addition, for each 10-year age increase, the odds of a rotator cuff tear increased 2.69-fold ($P = 0.005$).[34] Patients who are more than 60 years old and are exposed to prolonged quinolone antibiotics are at increased risk of Achilles tendonitis and tendon rupture.[116]

LIGAMENT

Ligament Structure

Ligaments connect bone to bone and thus stabilize, guide, and restrict joint motions.[3,26,36,46,54] Like tendons, ligaments function to resist tensile load.[46] Ligaments are composed of collagen type I (70% dry weight), elastin fibers, proteoglycans, and other minor collagens.[23] Collagen fibrils within each collagen fiber vary in size from 60 nm to 4000 nm in diameter.[35] The collagen fibers transfer the force within the ligaments.[64,84] The multiple collagen fiber bundles are interdigitated and function together to maintain normal joint motion.

Ligaments can be classified either as intra-articular or extra-articular. A majority of the research performed on ligaments has been on the anterior cruciate ligament (ACL), which is an intra-articular ligament. Mesenchymal stem cells have been found within the ACL.[96,100] The number of stem cells within the ligament decreases with age.[101] Stem cells have been found in both the ACL and the medial collateral ligament (MCL) of the knee, which is an extra-articular ligament. Zhang et al[127] found that the stem cells found in the ACL are intrinsically different from those found in the MCL, which may help explain why injuries to the MCL are commonly treated conservatively while injuries to the ACL require operative reconstruction to restore function. This concept of conservative management for extra-articular ligaments and operative reconstruction for intra-articular ligaments is related to the healing potential for each of the types of ligaments.

Vascular Supply

The microvascular circulation of the ACL and posterior cruciate ligament (PCL), intra-articular ligaments, is primarily from the infrapatellar fat pad and the synovial membrane, which form a vascular envelope with the vascular supply to the PCL greater than that of the ACL.[11] The ACL has a relatively hypovascular

segment in the central portion, which is common in intra-articular ligaments.[11] The ACL has been shown to contain a population of vascular-derived stem cells that may contribute to ligament regeneration and repair at the site of rupture.[76] In contrast to the ACL, the MCL is a relatively well-vascularized ligament, with high magnification histology revealing numerous capillaries in the substance of the MCL while there were none in the ACL.[109]

Biology of Ligament Aging

The ACL is subject to degeneration based on increasing age. Hasegawa et al[42] reported on the pattern of spontaneous age-related changes in the ACL in a histologic cadaveric study; ACL substance scores and ligament sheath inflammation scores increased with age. Collagen fiber disorientation was the most prevalent change that occurred earliest. Cadaveric human knee joints were evaluated histologically with special emphasis on the ACL, PCL, and cartilage.[68] The most significant histologic change was fiber disorientation, with only 6% of the intra-articular ligaments classified as normal and 76% showing mild degeneration.[68] There was a correlation between age and total histologic PCL scores and an even stronger correlation between age and total histologic ACL scores.[68] ACL cell metabolism has been previously studied; cell proliferation and migration are higher in skeletally immature animals[75] and an improved biomechanical response to healing was found in skeletally immature animals[79] possibly due to a decrease in growth factor receptor number with age.[107] In addition, with ACL cell maturity decreases in metabolic activity, collagen production and response to platelet-rich plasma occur along with an increase in apoptosis.[30]

Wang et al[110] studied the age-dependent changes in the matrix and organization of the ligament to bone insertion and found that there were age-dependent structural and compositional changes at the insertion site, with the skeletally immature group resembling articular cartilage while the adult interface resembled fibrocartilaginous tissue. There were marked differences in collagen fiber orientation that became more pronounced with age. The extracellular matrix composition and cellularity were also found to be age-dependent.[110] Normal aging results in decreased numbers and altered morphology of mechanoreceptors in the ACL, which correlates positively with the deficits in proprioception associated with aging.[15] Interestingly, the sulfur content in the ACL decreases gradually with aging whereas the content of calcium, phosphorus, and magnesium increased with aging.[103]

Biomechanics of Ligament Aging

Ligament biomechanics are also age-dependent. Murray et al[79] evaluated the biomechanical outcomes of ACL healing in skeletally immature and mature minipigs and found that immature animals healed the ligament better than mature animals. In addition, they found that the structural properties of the skeletally immature ligament were significantly better than those of the mature animal.[79] Woo et al[117] evaluated the structural properties of the femur-ACL-tibia complex in younger (22-35 years), middle aged (40-50 years), and older (60-97 years) knees and found that linear stiffness, ultimate load, and energy absorbed decreased significantly with specimen age. This correlates well with the original data from Noyes and Grood,[80] who found a decreased linear stiffness and ultimate load in the ACL with age.

Clinical Implications

ACL tears are a common problem in active patients, including both younger and older cohorts. In a recent study of second-look arthroscopy on double-bundle ACL reconstructions, synovial coverage was significantly decreased in elderly patients (50 years and older) as compared with either of the younger cohorts (29 years and younger; 30 to 49 years).[59] This alteration in synovial coverage was not reflected in clinical outcomes, which were not different between the age groups.[59] In addition, in a study evaluating the use of hamstring autograft, no difference in clinical outcome was found when comparing patients greater than 40 years old and a younger population.[73]

CONCLUSION

Tendons and ligaments are regularly arranged connective tissues with extremely important functions in the maintenance of joint stability and joint motion. With increasing age, these tissues are subject to vascular and compositional changes that alter their mechanotransduction, biology, healing capacity, and biomechanical function. Emerging theories, such as understimulation changing the mechanotransduction properties of the remaining tissue, will provide further information to help combat the age-related clinical complications associated with the injuries that occur to tendons and ligaments.

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