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Pathology of Chronic Achilles-Tendon Injuries in Athletes

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Overuse tendon conditions have traditionally been considered to result from an inflammatory process and were treated as such. Microscopic examination of abnormal Achilles-tendon tissues, however, reveals a noninflammatory degenerative process. The histopathology found in surgical specimens in patients with chronic overuse Achilles tendinopathy and those with Achilles-tendon rupture are reviewed. Seminal studies suggest that so-called tendinitis is a rare condition that might occur occasionally in the Achilles tendon in association with a primary tendinosis. These data have clinical implications and require a review of the traditional classification of pathologies seen in tendon conditions. The authors recommend that nomenclature be based on histopathological findings rather than traditional hypothesis.

Key Words: Achilles tendinopathy, Achilles-tendon rupture, histopathology, collagen, nomenclature, tendinitis

Key Points:

- Overuse tendon conditions have traditionally been considered to result from an inflammatory process and have been treated as such.
- It is suggested that the term *tendinopathy* be used as a generic descriptor that includes all pathologies that arise in and around tendons.
- Exercise protocols that aim to promote collagen repair might be the ideal therapeutic modality in this condition.

Introduction

Overuse tendon conditions have traditionally been considered to result from an inflammatory process and have been treated as such. Microscopic examination of abnormal tendon tissues, however, reveals a noninflammatory degenerative process.[1,2] New evidence suggests that so-called tendinitis is a rare condition that occurs occasionally in the Achilles tendon in

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association with a primary tendinosis. This article reviews the structure of normal tendon and then summarizes studies that examined the histopathology found in patients with medium- to long-term Achilles-tendon symptoms. Finally, recommendations are made to modify the diagnostic and descriptive nomenclature in patients with tendon disorders.

Normal Tendon Anatomy

This section briefly summarizes the macroscopic and light-microscopic appearance of normal tendon to better highlight the abnormalities found in symptomatic tendons. The reader is referred elsewhere for a more detailed description of tendon anatomy.[3,4]

Achilles-Tendon Architecture

The Achilles tendon connects the gastrocnemius, soleus, and plantaris muscles to the calcaneum. It transmits forces created in those muscles to bone to permit ankle plantar flexion.[4] As with all tendons, the basic elements of the Achilles tendon are collagen bundles, cells, and ground substance. Collagen is arranged in hierarchical levels of increasing complexity, beginning with tropocollagen, a triple-helix polypeptide chain, which unites into fibrils; fibers (primary bundles); fascicles (secondary bundles); tertiary bundles; and the tendon itself.[4-6] Collagen provides tendons with tensile strength. Ground substance (or extracellular matrix) is a viscous substance rich in proteoglycans that provides structural support for the collagen fibers and regulates the extracellular assembly of procollagen into mature collagen. Tenocytes are flat, tapered cells that are sparingly distributed among the collagen fibrils and synthesize both the ground substance and the procollagen building blocks of protein.[4]

The epitendon is a fine, loose connective-tissue sheath containing the vascular, lymphatic, and nerve supply. It covers the whole tendon and extends more deeply into the tendon between the tertiary bundles as the endotenon. More superficially, the epitenon is surrounded by paratenon, a loose areolar connective tissue consisting essentially of types I and III collagen fibrils, some elastic fibrils, and an inner lining of synovial cells.[7] Together, the paratenon and epitenon are sometimes called the peritenon.[4] A synovial tendon sheath consists of 2 layers and is only present in certain tendons as they pass through areas of increased mechanical stress. The outer layer is the fibrotic (ligamentous) sheath, and the inner layer is the synovial sheath, which consists of thin visceral and parietal sheets.[4]

The 2 other significant areas are the osteotendinous and myotendinous junctions. The osteotendinous junction is a specialized region in the muscle–tendon unit where the viscoelastic tendon transmits force into a rigid bone. The myotendinous junction is where tension generated by muscle fibers

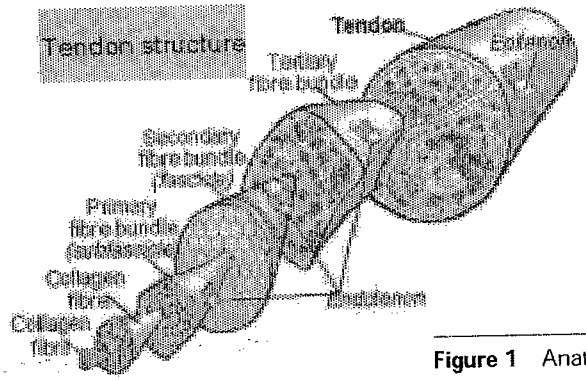

Figure 1 Anatomy of a normal tendon.

is transmitted from intracellular contractile proteins to extracellular connective-tissue proteins (collagen fibrils).[4] This region (with its complex ultrastructure) is rarely affected by tendinopathy.

Light-Microscopic Appearance of Collagen

Normal tendons appear glistening white. Microscopy, however, reveals dense, clearly defined parallel and slightly wavy collagen bundles. Collagen has a characteristic reflective appearance under polarized light. Between the collagen bundles, there is a fairly even but sparse distribution of cells with thin wavy nuclei. There is an absence of stainable ground substance and no evidence of fibroblastic or myofibroblastic proliferation. Tendon is supplied by a network of small arteries oriented parallel to the collagen fibers in the endotenon.[4,8] Autonomic nerves innervate these blood vessels, and this might play an important role in pathogenesis and tendon repair.[9,10] The light-microscopic appearance of normal tendon is the key outcome measure in studies of histopathology of overuse tendinopathies.

Histopathology Underlying Achilles Tendinopathy

In this section, findings are reported with regard to patients with Achilles-tendon problems not including clinical rupture, which are separate from findings in patients with ruptured tendons, even though there is substantial overlap in the pathologies underlying these 2 clinical conditions.

Achilles Tendinopathy Not Associated With Rupture

Histopathological study of symptomatic Achilles tendons reveals degeneration and a disordered arrangement of collagen fibers and an increase in vascularity.[11-20] There are at least 6 subcategories of collagen degeneration that have been described,[4] but Achilles-tendon degeneration is usually either

mucoid or lipoid.[4] Mucoid degeneration causes the affected region to soften, lose its normal glistening white appearance, and become gray or brown. Light microscopy reveals collagen fibers that are thinner than normal and large mucoid patches and vacuoles present between fibers. Alcian-blue-staining ground substance is increased. Lipoid degeneration is an abnormal accumulation of lipid in the tendon tissue.[4] The characteristic hierarchical structure of collagen fibers is also lost in degenerative Achilles tendons.[13,16,18,21,22]

There are many factors associated with the pathogenesis of a tendinopathic tendon. These include tissue hypoxia with consequent free-radical-induced tendon changes, resulting from ischemia-reperfusion injury, and exercise-induced hyperthermia.[23] Furthermore, a tendon that has been strained repeatedly to more than 4% of its original length loses elasticity and is at increased risk of subsequent break in collagen structure.[24] Tendons of older adults, on the other hand, exhibit little evidence of degeneration. Normal aging of connective tissue is morphologically different from degeneration.[16] Older tissue has a low rate of metabolism, progressively decreased elasticity, and lower tensile strength.

Astrom and Rausing,[25] in a landmark study of 163 patients (75% of whom participated in nonprofessional sports, particularly running) with classical symptoms and signs of Achilles tendinopathy for a median of 18 months (range 3 months to 30 years), reported an obvious change in collagen-fiber structure with loss of the normal parallel bundles (Figure 2). In subjects with macroscopically evident partial ruptures at surgery, fibrin deposits bordered frayed tissue, but the histopathology remained identical to those cases without rupture. Therefore it is recommended that these be called tendinopathy to reflect the identical pathology seen in overuse without any macroscopic evidence of rupture.

This type of Achilles-tendon degeneration is evident on MR imaging as increased signal[20,26-31] and on ultrasound hypoechoic regions.[14,30-32] These areas of abnormal imaging correspond with areas of altered collagen fiber structure and increased interfibrillar ground substance, which consist of hydrophilic glycosaminoglycans.[6,29,33]

With respect to the paratenon, Kvist et al[7,34,35] found mucoid degeneration, fibrosis, and vascular proliferation with a slight inflammatory infiltrate only—similar to other series.[13,17,18,36-38] Astrom and Rausing[25] found virtually no evidence of paratenonitis in their series of Achilles-tendon specimens. These differences might be explained by the fact that Kvist et al[7,34,39] did not report pathology of the tendon itself and studied more active, younger patients. Thus, paratenonitis is not a prerequisite for Achilles-tendon symptoms in a population of recreational sports participants and office workers. The major lesion in chronic Achilles tendinopathy "is a degenerative process characterized by the curious absence of inflammatory cells and a poor healing response."[25]

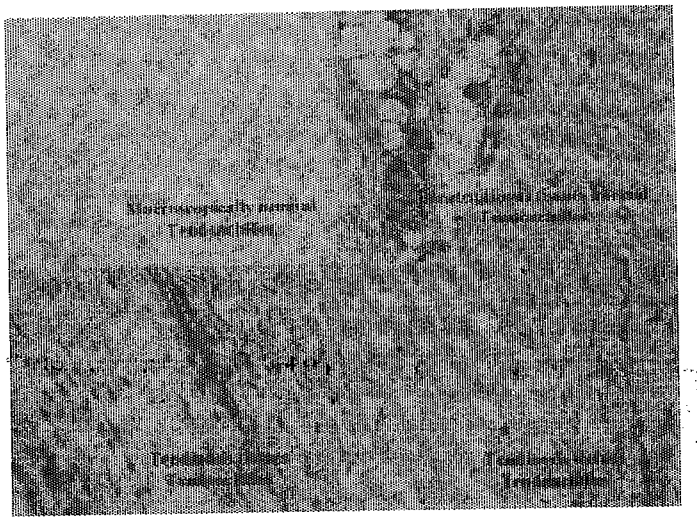

Figure 2 Normal and abnormal tendon stained with hematoxylin and eosin. Note the increased cellularity (blue nuclei) and disorganized collagen in the tendinosis tissue.

An important recent discovery indicates little biochemical evidence of inflammation in degenerative tendon tissue. Using a novel in vivo microdialysis technique first developed by Danish researchers for peritendinous use,[40-43] Alfredson et al, from Umeå in northern Sweden, performed intratendinous measurements (Figure 3) and showed that glutamate levels were elevated in painful, degenerative tendon but found no elevation in concentrations of inflammatory prostaglandin PGE2.[44,45]

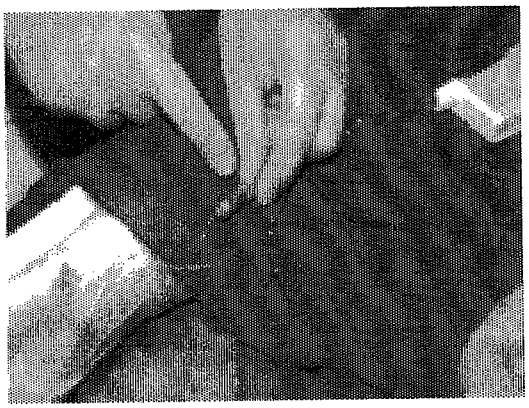

Figure 3 Microdialysis setup of Alfredson et al.[44,45] The microdialysis catheter has been threaded through the tendon substance to obtain intratendinous readings.

Histopathology in Achilles-Tendon Rupture

An important piece of background information is that histopathology of tissue from ruptured tendons is performed on abnormal tissue away from the site of the rupture.[46] Thus, the specimen provides information on the condition of the tendon immediately before rupture; it does not reflect the process of the rupture itself.

Histopathology of specimens taken from ruptured Achilles tendons revealed marked collagen degeneration and disorganization, increased cellularity and rounding of nuclei, and, in some specimens, hypervascularity that was not dissimilar to areas of degeneration in the nonruptured but symptomatic tendons described previously. Quantification of the histopathology,[47] however, demonstrates clearly that degeneration was more pronounced in ruptured tendons. There was an increased content of glycosaminoglycan in both the ruptured and the nonruptured, symptomatic tendons. The increase in extracellular matrix, coupled with the decrease in collagen fibers, showed an imbalance between the 2 structural components of the tendon tissue. It is uncertain which process came first. The increase in glycosaminoglycan content might be a result of mechanical overloading, and this, in turn, might affect the fiber structure and arrangement, leading to a reparative response with neovascularization. This imbalance between injury and repair leads to tissue damage.[16]

Tenocytes from ruptured Achilles tendons produce greater quantities of type III collagen than do tenocytes from normal Achilles tendons.[48] This might explain the histopathological differences seen, which would account for the tendon being less resistant to tensile forces and at increased risk of microscopic and macroscopic changes.

The findings in both the nonruptured and the ruptured tendons might result from a common, as yet unidentified pathological mechanism acting in both of these tendon populations. This hypothesis, however, does not explain why tendons that are histologically less degenerated cause marked pain, whereas tendons that rupture show a greater histopathological degree of degeneration despite not producing symptoms before the rupture.[2,49] This observation generates the hypothesis that 2 different pathological processes occur: 1 in patients who rupture their Achilles tendon without any previous pain and 1 in those who suffer from chronic tendinopathy pain.

Ackermann et al[9] have novel data that support a hypothesis that dysregulation of autonomic transmitters in hypovascularized tissues subjected to repetitive mechanical load might contribute to tissue hypoxia, leading to degeneration and rupture of tendons and ligaments. These data, and those of Alfredson[44,45] described previously, point to the need for further research into the biochemistry and immunohistochemistry of tendinopathies so that the mechanisms that underpin this condition can be better understood.

Clinical Implications

Because of the data described here, it has been suggested that the term *tendinopathy*[1,2,50,51] be used as a generic descriptor that includes all pathologies that arise in and around tendons. Tendinitis, tendinosis, and paratenonitis are specific examples of tendinopathy. Tendinitis refers to painful overuse inflammatory conditions, whereas paratenonitis is an inflammation of the outer layer of the tendon (paratenon), regardless of whether it is lined with synovium. Tendinosis, however, is collagen degeneration associated with increased ground substance (in the absence of inflammatory cells) and increased vascularity. There is no evidence that clinical examination can distinguish between tendinosis and tendinitis. A classification of overuse tendon conditions is summarized in Table 1.[1]

Table 1 Bonar's Classification of Overuse Tendon Conditions[1]

Pathologic diagnosis	Macroscopic pathology	Histologic finding
Tendinosis	Intratendinous degeneration commonly caused by aging, microtrauma, or vascular compromise	Collagen disorientation, disorganization, and fiber separation by increased mucoid ground substance, increased prominence of cells and vascular spaces with or without neovascularization, and focal necrosis or calcification
Partial rupture or tendinitis	Symptomatic degeneration of the tendon with vascular disruption, inflammatory repair response	Degenerative changes as noted above with superimposed evidence of tear, including fibroblastic and myofibroblastic proliferation, hemorrhage, and organizing granulation tissue
Paratenonitis	Inflammation of the outer layer of the tendon (paratenon) alone, whether or not the paratenon is lined by synovium	Mucoid degeneration is seen in the areolar tissue: a scattered mild mononuclear infiltrate with or without focal fibrin deposition and fibrinous exudate
Paratenonitis with tendinosis	Paratenonitis associated with intratendinous degeneration	Degenerative changes as noted in tendinosis, with mucoid degeneration with or without fibrosis and scattered inflammatory cells in the paratenon alveolar tissue

Conclusion

In summary, tendons are composed of connective tissue and are positioned between muscle and bone. Their main function is to transmit force. They are normally white and shiny and appear uniform in consistency under a microscope. There is an absence of stainable ground substance and no evidence of fibroblastic or myofibroblastic proliferation. The term *tendinopathy* is a generic descriptor that includes all pathologies that arise in and around tendons. Tendinitis, tendinosis, and paratendinitis are examples of tendinopathy. Histological studies show little evidence to support an inflammatory process happening in medical conditions traditionally labeled tendinitis. Actual tendinitis is rare, and tendinosis is common. Tendinosis is characterized at a cellular level by a degeneration and disordered arrangement of collagen fibers, an increase in vascularity and ground substance, areas of necrosis, and a distinct lack of inflammation.

Achilles tendons exhibit either a mucoid or a lipoid degeneration pattern of tendinosis. In symptomatic Achilles tendons, vascularity is increased and blood vessels randomly oriented, sometimes at right angles to collagen fibers. Inflammatory lesions and granulation tissue are infrequent and, when found, are associated with macroscopic evidence of partial ruptures. There is no biochemical evidence of inflammation in Achilles tendinopathy, but there is an increase of the neurotransmitter glutamate. Thus it is recommended that clinicians consider overuse Achilles tendon injuries to be essentially caused by tendinosis, and there appears to be little biological rationale for using pharmaceuticals or physical modalities that aim to reduce inflammation in these conditions. Exercise protocols whose goal is to promote collagen repair might be the ideal therapeutic modality in this condition.

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