

SECTION III

REGULAR AND SPECIAL FEATURES

Biomechanical Basis for Tendinopathy

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Tendinopathy affects millions of people in athletic and occupational settings and is a nemesis for patients and physicians. Mechanical loading is a major causative factor for tendinopathy; however, the exact mechanical loading conditions (magnitude, frequency, duration, loading history, or some combinations) that cause tendinopathy are poorly defined. Exercise animal model studies indicate that repetitive mechanical loading induces inflammatory and degenerative changes in tendons, but the cellular and molecular mechanisms responsible for such changes are not known. Injection animal model studies show that collagenase and inflammatory agents (inflammatory cytokines and prostaglandin E₁ and E₂) may be involved in tendon inflammation and degeneration; however, whether these molecules are involved in the development of tendinopathy because of mechanical loading remains to be verified. Finally, despite improved treatment modalities, the clinical outcome of treatment of tendinopathy is unpredictable, as it is not clear whether a specific modality treats the symptoms or the causes. Research is required to better understand the mechanisms of tendinopathy at the tissue, cellular, and molecular levels and to develop new scientifically based modalities to treat tendinopathy more effectively.

Tendons transmit muscular forces to bone. As a result, tendons are subjected to mechanical loads. Similar to other connective tissues such as bone, tendons alter their structure and composition in response to changes in mechanical loading conditions. As a result of this adaptive

response to mechanical forces, tendons also are susceptible to pathologic changes.^{32,84,139} To describe the pathologic conditions of tendons, numerous terms have been used (Table 1), which reflects our poor understanding of the pathogenesis of tendinopathy. For example, the term tendinitis, or tendonitis, is used to describe tendon inflammation, whereas the term tendinosis describes asymptomatic tendon degeneration with various histologic features.^{31,69,133} The term tendinopathy also has been proposed.¹¹⁰ This term provides a generic descriptor of clinical conditions affecting tendons, characterized mainly by a combination of pain, swelling, and impaired performance. Therefore, it has been suggested that the terms tendinitis (tendonitis) and tendinosis be used only after biopsy and histopathologic confirmation.^{110,131,139}

Tendinopathy is a serious health problem for people in occupational and athletic settings.^{15,72,109,112,131} Many occupational activities result in development of tendinopathy with clinical symptoms, including pain and signs of inflammation (such as swelling), which impair the ability to work.¹³¹ Furthermore, participation in recreational sports activities has increased during the past few years,^{12,112} which, in addition to a sedentary lifestyle, has contributed to a greater incidence of tendinopathy in the general population. The etiology of tendinopathy is considered to be multifactorial,^{84,106,131,139} and the pathogenesis of tendinopathy is unclear.^{139,148} However, numerous studies have shown that mechanical loading plays a major role in the development of tendinopathy. With this theme in mind, we will review published studies based on the following considerations: (1) established work in tendon biomechanics; (2) studies that used implantable devices to measure in vivo mechanical loads of tendons that are susceptible to repetitive motion injuries, including the Achilles tendon, patellar tendon, and finger flexor tendon; (3) established work regarding the training effect on changes in the tendon's mechanical properties and the production of inflammatory mediators, including lipid prod-

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TABLE 1. Terminology for Pathologic Conditions of Tendons

Term	Definition	Reference
Tendinitis or tendonitis	Tendon inflammation	15, 40, 43, 99, 145
Tendinosis	Asymptomatic tendon degeneration	69, 133
Tendinopathy	Generic descriptor of tendon disorders	81, 110, 139
Paratenonitis	Inflammation of the paratenon	69, 72, 110
Peritendinitis (tenosynovitis, tenovaginitis)	Inflammation of the peritendon (peritenon and tendon sheath)	72, 110
Spontaneous tendon rupture	Rupture without any preinjury signs or symptoms	74
Partial rupture	Partial tear of the tendon	76, 77, 110, 134
Enthesopathy or enthesitis	Tendon-bone junction disorders	31, 90, 110

ucts [eg, prostaglandin E₂ (PGE₂)] and degradative enzymes [eg, matrix metalloproteinase-1 (MMP-1)]; and (4) animal models of tendinopathy used to study the biologic effects of repetitive mechanical loading and agents, including collagenase, cytokines, and prostaglandins, on the tendons.

In selecting clinical studies for review, we considered whether the studies involved a large number of patients and whether there was long-term followup, whether the studies were retrospective or perspective, whether they were randomized and had control groups in their design, and whether the studies were based on the findings of basic science research.

Although we strove to provide an overview of the literature regarding the biomechanical basis for tendinopathy and the current treatments and provided limitations in these regards in the literature, we did not attempt to assess the quality of individual studies cited in this review. A recent review¹⁷⁵ provides a general description of tendon mechanobiology, including the mechanobiologic responses (eg, training and disuse effects on tendons) and healing process of traumatically injured tendons, and a discussion of cellular mechanotransduction mechanisms. In this review, we discuss the role of mechanical loading in the genesis of tendinopathy at the tissue, cell, and molecular levels, evaluate current treatment options for tendinopathy from the biomechanical perspective, and offer future directions for research of tendinopathy and potential treatment options based on basic science research for clinical management of tendinopathy.

Mechanical Behavior of Tendons

The mechanical response of tendons can be characterized by its stress-strain curve, which is obtained by in vitro mechanical testing of tendon specimens.³⁶ A typical tendon stress-strain curve has three phases (Fig 1). In the resting phase, tendons have a wavy or crimped configuration because of the crimped shape of collagen fibers, which disappears when the strain exceeds 2%. After this initial toe region of as much as 4% strain, the tendon can

return to its original length. Between 4% and 8% strain, there are microscopic collagen fiber ruptures. Beyond this level of strain, there are macroscopic tears, which eventually lead to complete tendon rupture at approximately 12% strain.^{36,43,72} These classic values of tendon strains, however, could be underestimated. Using a modern testing technique, Devkota and Weinhold reported that avian flexor tendons can be stretched elastically as much as 14%.⁴⁶

There is a large gap between strains experienced in vivo during physiologic activities (less than 4%) and strains that cause tendon failure. Tendons usually are loaded as much as 1/4 or 1/3 of the ultimate tensile load before the tendon ruptures.^{48,87,116} However, repetitive submaximal loading can cause microscopic injuries to collagen fibrils or fibers, which reduce the effective cross-sectional area of the tendon for transmitting muscular forces.¹²¹ Consequently, these microscopic injuries make the tendons more susceptible to failure.⁸³

In addition to the strain level, strain rate is an essential parameter to characterize the mechanical behavior of tendons because they are a viscoelastic material.^{36,65,114,170} Therefore, tendons are easily deformed at low strain rates. As a result, tendons absorb more energy but are less effective in transmitting loads. At high strain rates, they become stiffer and less deformable but are more effective in moving large loads in vivo.

Mechanical Loads of Tendons

Tendons (eg, Achilles tendon and patellar tendon) transmit muscular forces, and as a result, are subjected to tensile forces. However, compressive and shear forces also act on some tendons, including the rotator cuff, the long head of the biceps tendon, the extensor carpi radialis brevis, and the tibialis posterior.^{16,43}

To understand pathophysiologic features of tendons, it is necessary to determine the mechanical forces acting on tendons during normal activity. Therefore, tendon forces in vivo in animals and in humans were measured using implantable devices,^{49-51,86,137,146} or estimated using non-

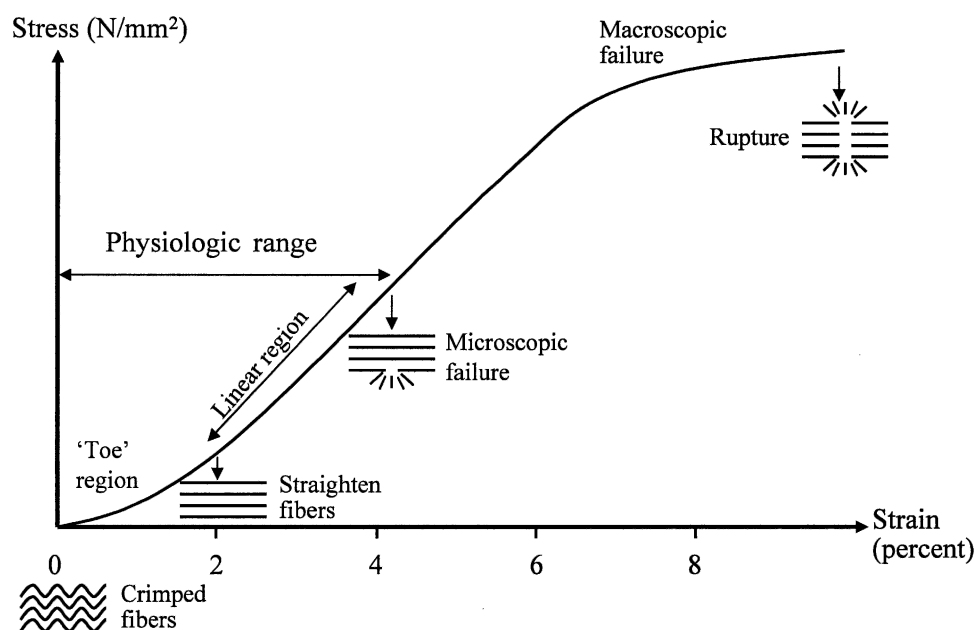


Fig 1. The mechanical response of the tendon is defined by the stress-strain curve. With increased strain levels, the tendon risks being injured from microinjuries at small strains (4% to 8%) to complete rupture (> 12%). (Adapted with permission from Wang JH. *Mechanobiology of tendon. J Biomech.* July 4, 2005 Epub ahead of print.)

invasive imaging techniques, such as ultrasonography and magnetic resonance imaging.^{66,92,114,115,123,149,172,173}

Using an implantable force transducer, the force on the patellar tendon in adult goats was measured during various activities. It was found that the average patellar tendon force was 207 N during standing, but it reached a maximum of 800 N during walking and 1000 N during trotting.⁸⁷ In rabbits, forces on the Achilles tendons increased from 16.3 N during rest to 57.7 N and 76.6 N during level and inclined hopping, respectively. It also was reported that peak tensile forces increased significantly with inclination (0°–12°) and that the rate of change in tendon forces increased significantly with speed (0.04–0.13 m/second) and inclination.^{73,180} In human subjects, Achilles tendon forces during walking, running, and jumping have been measured. The Achilles tendon forces reached a maximum of 9 kN when the subject ran at 6 m/second, which corresponded to forces equal to 12.5 times the body weight.⁸⁶ In another study, it was found that in the breaking phase of contact in running, maximum Achilles tendon forces were 1608 N and 1758 N at speeds of 3 m/second and 5 m/second, respectively.⁹² Also, using an optic fiber technique, the peak Achilles tendon force was measured at three speeds (1.1, 1.5, and 1.8 m/second) and found to be 1430 N on average, which was rather insensitive to walking speed (1320, 1480, and 1490 N for 1.1, 1.5, and 1.8 m/second, respectively). On the contrary, the rate of Achilles tendon force development increased 32% from slow to

fast walking speeds (6570 to 9670 N/second for 1.1 m/second to 1.8 m/second, respectively).⁵¹ In addition, the influence of a specific activity on the forces of different tendons was studied. It was estimated that the patellar tendon force produced during squat jumping was 3200 ± 1463 N, whereas the Achilles tendon force was 1305 ± 811 N.⁵⁰

In addition to tensile loads, compressive loads act on some tendons such as the rotator cuff, which is subjected to compression perpendicular to the tendon.³² These tendons change direction by passing under pulleys or retinacula. At these sites, tendons are subjected to compression and also shearing forces. It was estimated that this compressive force is approximately twice that of the tension in the tendon multiplied by $\frac{1}{2}$ the sine of the angle through which it changes direction.¹⁸

Arndt et al,²² in an in vivo study, examined the occurrence of nonuniform forces over Achilles tendon substance during isometric plantar flexion at nine different knee angles. Using an implantable optic fiber technique, the gastrocnemius and soleus muscles were found to contribute separately under individual activation patterns in tensile force of Achilles tendons. A force discrepancy of 967 N was measured between these two muscles, which corresponds to a stress discrepancy of 21 N/mm² over the cross-sectional area of the Achilles tendon. This indicates that different loads act on different parts of the tendon at the same time. Consequently, apart from these different

tensile loads, additional frictional forces exist between these adjacent intratendon sections and their collagen fibers, which may represent an additional mechanism that causes tendon injury.

Moreover, the position of the adjacent joint influences generation of tendon forces. Flexor tendons in the fingers withstand tensile forces ranging from 0.7 to 3.2 times the fingertip key strike during typical piano key strike positions. However, Harding et al found that flexor tendon tension is reduced using a curved finger position with a large metacarpophalangeal joint flexion angle and a small proximal interphalangeal joint flexion angle.⁶¹

Therefore, several factors affect the mechanical forces that act on tendons in vivo. First, tendons at different locations in the body are subjected to different levels of mechanical loads. A typical example is the Achilles tendon, which withstands greater tensile forces than those of the tibialis anterior.^{114,115} Second, the mechanical stress of the tendon depends on the level of muscle contraction and the tendon's relative size. For example, the greater the cross-sectional area of a muscle, the greater the force it produces and the larger the tendon stress (eg, patellar tendon versus hamstrings tendons). Third, different types of activity also induce different levels of forces on tendons.^{22,73,87,116} Similarly, varying the rate and frequency of mechanical loading result in different levels of tendon forces.^{51,92} Finally, stance or motion of the adjacent joint and activity of the antagonist muscles influence the magnitude of tendon forces.^{61,101,102}

Biologic Response of Tendons to Mechanical Loading

It is known that the structure, composition, and mechanical properties of the tendon change in response to altered mechanical loading conditions.^{168,169} For example, in rabbits, 40 weeks of training increased the ultimate load at failure of the peroneus brevis tendon.^{168,169} In other animal models, long-term training or exercise enhanced the strength of the insertion site of digital flexor tendons¹⁸³ and the cross-sectional area (164% after 16 weeks), but decreased the maximum stress of failure (51% to 63% of control value).¹⁵⁴ In addition, vigorous exercise in trained athletes was found to induce the net production of collagen Type I in the Achilles tendon.^{93,94,96} However, stress deprivation by immobilization for a certain period decreased the tendon's total weight, stiffness, and tensile strength.^{17,162,163,184}

Although appropriate training or exercise produces positive effects on tendons, excessive loading of tendons during vigorous physical exercise, such as application of a very high mechanical load or a low but repetitive mechanical load with a high frequency and/or long duration, may induce tendon degeneration.^{138,147} In rats, 4 weeks of extensive training decreased the elastic modulus of the su-

praspinus tendon to 52% of the control value. Extensive training also decreased the maximum stress of failure to 51% of the control value.¹⁵⁴

In vivo measurements in human Achilles tendons indicate a remarkable increase of inflammatory mediators in response to exercise. Prostaglandin E₂ and thromboxane B₂ increased from 0.6 ng/mL and 4.8 ng/mL at rest to 1.4 ng/mL and 8.1 ng/mL during exercise, respectively. Prostaglandin E₂ and thromboxane B₂ still increased after a recovery period of 60 minutes (1.3 ng/mL for PGE₂ and 5.9 ng/mL for thromboxane B₂).⁹⁵ These activities could be a part of normal tendon response to mechanical loading, but excessive production of PGE₂ could be a contributing factor to the onset of tendinopathy.^{104,176}

Conversely, in other studies, no significant changes were found in the amount of PGE₂ in the Achilles tendon, patellar tendon, or extensor carpi radialis in healthy human subjects or in subjects with clinical symptoms of tendinopathy.^{3,5,6,11} However, these measurements were done on a small number of subjects (four patients with chronic Achilles tendinosis, five patients with chronic patellar tendinosis or jumper's knee, and four with tennis elbow), mostly during resting periods. The measurements also had large variations, which reduced statistical power.

Substance P and glutamate also have been reported to have nociceptive activity in animal and human tendons.^{2,4,5,11} Rats were subjected to eccentric exercise of the hind paw three times a week for 1 hour while under general anesthesia to induce Achilles tendon disorders. Tendons from the exercised limb showed, in the majority of cases, hypervascularization, an increased number of nerve filaments, and increased immunoreactivity for substance P and calcitonin gene-related peptide, compared with tendons from the nonstimulated limbs, which looked normal.¹¹⁹ In humans, patients with tennis elbow were found to have increased immunoreactivity of substance P and calcitonin gene-related peptide at the origin of the extensor carpi radialis brevis muscle.¹⁰⁵ Therefore, it has been suggested that frequent mechanical loading affects the production of the substance P and calcitonin gene-related products, and these substances may mediate adaptive responses to mechanical strain, including nociception, microvascular leakage, local edema formation, and tendon matrix gene and enzyme (eg, MMP-1) modulation.^{1,57,62,63,105}

The modulation of MMP-1 gene expression also was studied in rat tail tendons in culture.²³ Increasing static tensile stresses as much as 2.6 MPa gradually inhibited the MMP-1 mRNA expression, whereas stress-deprivation for 24 hours resulted in a significant up-regulation of MMP-1 expression. Arnoczky et al²³ also reported that a 1% strain decreased MMP-1 mRNA expression, whereas 3% and 6% strain completely inhibited it. This strain effect on

MMP-1 mRNA expression was dependent on stretching frequency.⁹⁷

Because tendon fibroblasts are a dominant cell type in tendons, there is little doubt that these cells are primarily responsible for the tendon's physiologic or pathologic changes in response to mechanical loads. Fibroblasts in tendons are linked via actin-associated adherent gap junctions along the tendon long axis.¹³⁵ The presence of a three-dimensional network of cells in tendons, via cell processes and gap junctions, facilitates cell to cell communication, which allows cells to detect and coordinate their responses to mechanical loads.^{27,118,165} These adaptive cellular responses lead to the remodeling of tendon structure²⁸ and affect reparation and remodeling of injured tendons.¹⁷¹ However, the cellular biologic response to mechanical loading conditions may lead to pathophysiologic changes in tendons, such as tendinopathy (Fig 2).⁹⁹ This possibility was seen in some in vitro studies. For instance, repetitive mechanical loading of human tendon fibroblasts alters cell proliferation and collagen synthesis¹⁸⁵ and affects MMP-1 and MMP-3 gene expression and COX-2.²⁰

Mechanical stretching of human tendon fibroblasts also increased production of PGE₂ and LTB₄.^{13,14,176} Because PGE₂ and LTB₄ are known to be present in inflamed or injured tissues such as tendons, it is thought that they may be involved in the development of tendinopathy.^{82,104,176}

However, there are some limitations in these studies,^{13,14,176} including lack of an extracellular matrix surrounding the tendon fibroblasts in these culture models, and an unclear understanding of how these loading protocols represent in vivo situations, such as low magnitudes of mechanical loads with repetitive application (eg, training and exercise). Nevertheless, the cellular production of inflammatory mediators such as PGE₂ seems consistent with those from human subject studies under repetitive mechanical loading conditions.⁹⁵

Although the magnitude of mechanical loads on tendons is crucial in the induction of pathophysiologic changes of the tendon such as tendinopathy, the manner and history of loading are equally important. A mechanical overload of tendons can be caused not only by a large magnitude of stress, but also as a result of a tensile force

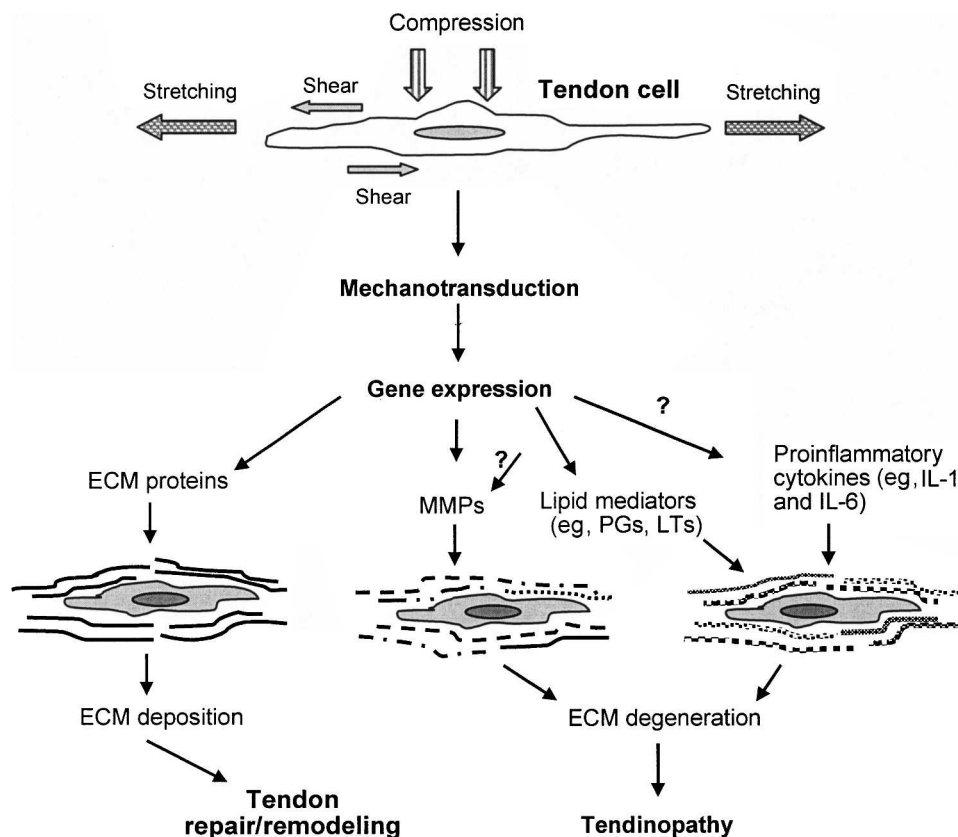


Fig 2. The biologic responses of tendon fibroblasts to repetitive mechanical loading conditions are shown. Depending on mechanical loading conditions, the cellular mechanobiologic responses may lead to tendon physiologic remodeling or pathologic changes such as tendinopathy.

exerted at a high rate and short duration. Similarly, long-term repetitive loading may have accumulative effects on tendons, such as microinjuries and production of inflammatory mediators (eg, PGE₂ and LTB₄), nociceptive factors (eg, substance P), and degradative enzymes (eg, MMP-1 and MMP-3). Collectively, these may result in tendon overuse injuries even if these loads are within the strength limits of the tendon.^{48,71,72,84,85} In addition, repetitive compressive overloading can produce overuse injuries in compressed tendons (eg, rotator cuff, long head biceps, and flexor hallucis longus).^{19,35,153,154,167,181} Also, mechanical loading is only one factor in the development of tendinopathy; other factors such as vascular supply, age, and genetics also can participate in its pathogenesis.¹³⁹ This may explain why tendinopathy also occurs in sedentary people.^{164,186}

Animal Model Studies of Tendinopathy

Efforts have been made to create animal models of tendinopathy. In rabbits, after passive exercise for 5 to 6 weeks on the hind paw, with a rate of 150 flexions and extensions per minute for 2 hours, three times a week, there were degenerative changes in the Achilles tendon, including an increased number of capillaries and increased infiltration of inflammatory cells, edema, and fibrosis in the paratenon.²⁶ In another study, a voluntary forelimb repetitive reaching and grasping task in rats was evaluated. After rats reached for food at a rate of 4 reaches/minute for 2 hours/day and 3 days/week for as much as 8 weeks, it was found that the number of macrophages increased markedly in the tendons of the upper extremity and collagen fibrils became frayed.²⁹ Finally, in a treadmill study using rats,¹⁵⁴ it was found that the number of cells in the supraspinatus tendon increased, and collagen fibers became disorganized and damaged at 8 weeks. In addition, cross-sectional area of the tendon increased significantly but maximum stress decreased significantly. These results suggest that repetitive mechanical loading of tendons causes tendon inflammation and destruction via mechanical damage, biochemical mediators, or more likely, both.¹⁷⁵

Because of the cost and sometimes inconsistent results of exercise animal models for tendinopathy,²¹ efforts have been made to develop injection animal models. One such model involves injecting bacterial collagenase into animal tendons.^{44,64,151,152} For instance, it was found that collagenase injection caused infiltration of lymphocytes and macrophages and disruption of collagen matrix in tendons.⁶⁴ This type of animal model seems to represent a typical tendon healing response attributable to a traumatic insult to the tendon, which is contrary to the fact that development of tendinopathy is an insidious process and the tendon with tendinopathy often does not heal.^{139,148}

In another study, cell activating factor (CAF), which is composed of inflammatory cytokines [eg, interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF)] and other unknown factors, was used for injections in rabbit patellar tendons.¹⁵⁷ It was found that injection of CAF increased cellularity around the injection site and decreased failure loads of the patellar tendons. However, there are some limitations to this model. First, the CAF in the model was produced by synovial fibroblasts in response to phorbol myristate, an inflammatory agent, and not in response to repetitive mechanical loading. It is likely that the factors produced by mechanically stimulated tendon fibroblasts would be different from the CAF produced by chemically treated synovial fibroblasts. Second, the exact composition of the CAF was unknown; therefore, the model may be difficult to reproduce. This limits the reliability of its use in studying the developmental mechanisms of tendinopathy. Third, because the CAF is not defined, it is not clear from this model which factors are responsible for the development of tendinopathy.

Because it is known that tendons or tendon fibroblasts produce inflammatory mediators in response to mechanical loading as shown in *in vivo* and *in vitro* investigations,^{13,95,104} studies have been done in which inflammatory agents were injected into animal tendons. In one such study, a peritendinous injection of PGE₁ around the rat Achilles' tendon was found to induce inflammation and degeneration around and within the tendon.¹⁵⁸ A subsequent study showed that injection of PGE₂ into the mid-substance of the tendon induces profound degenerative changes in the tendon matrix.⁸² Because PGE₂ induces metalloproteinase synthesis and inhibits collagen synthesis in fibroblasts,^{41,166} it is possible that the production of PGE₂ may be an upstream event before collagenase production in tendons subjected to repetitive mechanical loading.

Although these studies showed that the injection animal model is a reliable, cost-effective approach to studying the molecular mechanisms of tendinopathy, use of the injection animal model may be improved by using multiple inflammatory mediators that are biologically produced by tendon fibroblasts in response to various mechanical loading conditions. In addition, if a tendon with microinjuries undergoes the same healing response as that of traumatic injuries, proinflammatory cytokines such as IL-1 β and TNF- α should be considered in the injection animal model.

Treatment Options for Tendinopathy

Because the pathogenesis of tendinopathy is not well understood, how to treat it is debatable. Nonoperative, conservative treatment is the initial and most-recommended approach.^{8,10,43,72,80,91,144,179} First and foremost, the goal

is to relieve the symptoms and then, if possible, to identify and correct any causative factors.⁷ However, many conservative and surgical treatments are based largely on empirical experience and attempt to control or enhance the tendon's healing response.^{72,144}

Structural damage in tendinopathy may include partial tearing of the collagen fibers; therefore, rest offers time for the tendon tissue to heal. However, lower tendon metabolic activity (only 13% of the oxygen uptake of muscle) causes an extended healing period.¹⁸⁷ In addition, it has been postulated that tissue damage already is advanced when the symptoms appear, therefore, more rest is needed to allow enough time for injured tendons to repair.⁹⁸ If the clinical condition is not severe (eg, mild pain, swelling, and tenderness), the advice may be to simply decrease the intensity, frequency, and duration of the activity that caused the injury.¹⁰⁹ Because controlled mobilization enhances the tendon's structural and mechanical properties,^{162,171,184} Stanish et al suggested the "drop and stop" regimen, which implies a gradual increase of the speed and intensity of exercises as the pain disappears.¹⁵⁶

Nonsteroidal antiinflammatory drugs (NSAIDs) are the most frequently used pharmacologic substances for treatment of tendinopathy.^{99,103,125,143,178,179} Healing of acute soft tissue injuries is slightly more rapid, and inflammation might be better controlled with the use of NSAIDs.¹⁷⁸ However, although the efficacy of NSAIDs is controversial, the possibility remains that NSAIDs could benefit patients because they reduce tendon inflammation.^{12,177} In addition, NSAIDs are known to reduce pain and therefore, have been used for short periods to facilitate rehabilitation after tendon injuries.¹⁴⁴

The role of corticosteroids in the treatment of tendinopathy also is controversial.^{15,80} Some investigators observed that intratendinous injections of corticosteroids led to cell death, tendon atrophy, and negative mechanical effects (eg, reduced tensile strength and loss of viscoelasticity) on tendons.^{78,128} However, Kannus and Jozsa found that there were no greater pathologic changes in ruptured tendons that had received corticosteroid injections when compared with tendons that had not received injections.⁷⁴ Therefore, efficacy of corticosteroid injections for treatment of tendinopathy remains unclear.¹⁵⁰

Some other pharmaceutical agents, such as aprotinin (a protease inhibitor) and glycosaminoglycan polysulphate, one of the constituents in ground substance, also have been proposed in therapies for tendon disorders.^{37,38,47,159} Based on the hypothesis that neovascular development in a chronically painful tendon is accompanied by proliferation of nerves that are responsible for the pain, sclerosing agent injections were administered to Achilles tendons with tendinopathy and relieved pain.^{3,129}

Furthermore, training errors^{33,34,68,179} and improper equipment (eg, athletic shoes, skis, racquets)^{33,34,70} reportedly can cause mechanical overloading of tendons. Therefore, correct technique, equipment, braces, and supports are used to decrease the load that is placed on the tendon.

Other modalities such as ultrasound, laser photostimulation, deep heat, pulsed magnetic and electromagnetic fields, and electrical stimulation also are used to treat tendinopathy.^{43,54,58,100,130,140} Application of these modalities is intended to affect the stiffness of newly formed scar tissue inside the tendon, either through the mechanical effect of high-frequency sound waves or increase of local heat and blood flow. In addition, there is evidence that ultrasound treatment increases collagen synthesis of tendon fibroblasts and enhances tensile strength of the healing tendon.^{67,144} After Achilles' tenotomies in rabbits, collagen concentration in tendons that had received laser photostimulation increased by 26%, compared with controls.¹³⁶ Tasto et al proposed that bipolar radiofrequency can be used on the basis of its ability to stimulate angiogenesis and regulate various growth factors.¹⁶⁰ Based on studies that proved the analgesic effect of an extracorporeal shock wave, use of this technique was proposed as an alternative for alleviation of tendinopathy symptoms.^{39,55,142,155,174} However, the effectiveness of these treatment modalities is questionable as their results are controversial, especially regarding long-term clinical benefits.^{72,140}

A remarkable treatment for tendinopathy is stretching and strengthening, particularly eccentric exercise. This modality has been advocated as part of the treatment for tendinopathy since the 1980s.^{42,43,156} Heavy loading of a tendon in a chronic tendinopathy condition has been reported to provide relief of symptoms.^{3,7,8,113} It is not clear, however, how applying forces to a chronically overloaded and painful tendon can benefit the tissue. One suggested mechanism is that mechanical loading with certain magnitudes and frequencies enhances tendon repair and remodeling by stimulating fibroblast activities (eg, increased collagen synthesis).⁷⁵

When conservative treatments are not effective, operative treatment for tendinopathy is considered. The choice of operative treatment depends on the patient's age, duration of symptoms, and occurrence of histologic changes.⁹¹ There are numerous surgical options. The excision of the macroscopically hypertrophic pieces or the abnormal sites inside the tendon substance after a longitudinal tenotomy is one option.^{9,99,122,127,145,182} Multiple percutaneous incisions at the site of the disease also have been used to increase blood circulation, enhance oxygen uptake, and induce migration of macrophages, which remove damaged cells and extracellular matrix (ECM) and release growth factors. This, in turn, stimulates fibroblast proliferation

and collagen synthesis.¹¹¹ Nirschl proposed that good surgical results should achieve resection of the pathologic tissue, maintenance of attachment of normal tissues, and good postoperative rehabilitation.¹²⁸

DISCUSSION

Tendinopathy is a common problem for professional and recreational athletes. There is also an increased incidence of tendinopathy in occupational settings.^{30,59,72,109,161} Numerous studies have been devoted to investigating tendinopathy.¹⁵ Consistent findings of these studies include tendon inflammation, mucoid degeneration, and fibrinoid necrosis in the tendon. Microtearing and areas of repair with proliferation of the tendon fibroblasts and thin-walled vessels also have been observed.^{80,117} These studies, however, are limited in that the understanding of tendinopathy is based primarily on histologic analyses of human tissue samples taken during surgery. Therefore, they do not shed light on the developmental mechanisms of tendinopathy at the cellular and molecular levels.

Exercise animal models have been developed to study the effect of repetitive mechanical loading on tendons. Studies using these animal models showed that tendons that were repetitively loaded were grossly inflamed, infiltrated with inflammatory cells, and had an increase in vascularity²⁶ and degenerative changes.¹⁵⁴ Although there are inconsistent data from exercise animal model studies,²¹ these studies in general confirm the crucial role of repetitive mechanical loading in the development of tendinopathy.²⁹ However, these animal studies are limited in that cellular and molecular mechanisms responsible for development of tendinopathy cannot be deduced.

Efforts also have been made to develop injection animal models to study tendinopathy.^{44,64,82,151,152,157,158} Studies using these animal models showed that injection of collagenase, PGE₁, and PGE₂ caused tendon inflammation and degeneration; however, there is still uncertainty regarding whether these factors are produced physiologically by tendon cells *in vivo* under repetitive mechanical loading conditions and whether they are individually or collectively responsible for onset and progression of tendinopathy. In addition, determination of physiologic dosages of these agents for injections is a challenge.

As indicated in this review, repetitive mechanical loading is considered one of the major causative factors in the development of tendinopathy. However, although there are numerous published studies in which mechanical forces of tendons have been measured during various activities, there are few studies that have investigated the influence of different mechanical loading conditions (magnitude, frequency, duration, or loading history) on the occurrence of tendinopathy.

Also, it generally is thought that mechanical loading induced tendinopathy via tendon microinjuries. Although this premise is intuitively reasonable, little scientific data exist to support it. Therefore, studies examining whether such tendon microinjuries exist should be done on an animal model under repetitive mechanical loading conditions using novel noninvasive technology. If microinjuries in tendons exist, then we should examine whether tendon microinjuries trigger the same healing response as traumatic injuries to tendons and the effects of continued repetitive mechanical loading on the tendon's healing response.

Furthermore, although it is known that repetitive mechanical loading causes structural and biochemical changes in tendons, such as induction of inflammatory mediators and collagen degradation,^{11,29,79,95,124} whether mechanical loading interacts with intrinsic factors (eg, age and blood supply) to trigger the onset of tendinopathy is not known. Additional research is necessary.

To better understand the mechanisms that cause tendinopathy, the effects of different mechanical loading conditions (eg, stretching magnitude, frequency, and duration) on collagen and other ECM structural protein synthesis in intact tendons, the role of mechanical loads in the repair of injured tendons,^{27,88} the interaction between the production of inflammatory mediators (eg, PGE₂ and IL-1 β) and mechanical loading in inflamed or injured tendons, and the combined effects of drug treatment and tissue engineering approaches (see below) with a loading protocol such as eccentric exercise should be studied.^{42,43} Additionally, although *in vivo* measurements of tendon forces provide data at a specific time during the tendon's pathogenetic process, the measurement interferes with the results if it is invasive (eg, implanted mechanotransducers). Therefore, noninvasive approaches must be devised to monitor the developmental process of tendinopathy on an animal model.

Effective protocols to treat tendinopathy also must be developed. Current nonsurgical treatment regimens for tendinopathy, including NSAIDs, corticosteroids, and physical therapy, offer only largely temporary relief of symptoms (eg, pain). Some surgical techniques for tendinopathy have been proposed, but none offers consistent results.^{127,132,141,145} Additionally, numerous studies regarding efficacy of new modalities for tendinopathy were retrospective, had a small sample size, or had short-term followup.^{10,38,55,113,129,130,155,160}

A few possible treatment options that have been proposed include application of growth factors that stimulate cell proliferation and ECM synthesis in tendons with tendinopathy.^{56,60,120,126} Injection of insulinlike growth factor-I (IGF-I) in injured or degenerative animal tendons increases collagen synthesis and improves functional prop-

erties, such as improved walking pattern.^{44,89} Cartilage-derived morphogenetic protein-2 (CDMP-2) was shown to increase the ultimate tensile strength of injured tendons after transection.⁵² Bone morphogenetic proteins (BMP-13 and BMP-14) were shown to increase the amount of tendon callus in transected rat Achilles tendon,²⁴ and recombinant BMP-12 added to human patellar tendon fibroblast cultures increased cell proliferation and gene expression of procollagen Types I and III.⁵³ Gene therapy can be used to improve the tendon's structural properties.^{107,108} Mesenchymal stem cells²⁵ and small intestinal submucosa⁴⁵ were used to treat injured tendons in animal models and showed promising results. These tissue engineering approaches may be useful to promote or enhance healing of degenerative tendons during the late phases of tendinopathy and enhance their structural and mechanical properties.

Appropriate mechanical loading conditions for optimal efficacy of the above approaches to treat tendinopathy should be investigated. It is our opinion that mechanical loads with inappropriate loading magnitudes, durations, and frequencies are major causative factors in the development of tendinopathy. However, our understanding of the biomechanical basis for development of tendinopathy is incomplete. Research is needed to elucidate the role of mechanical loading in the pathogenesis of tendinopathy at the tissue, cellular, and molecular levels so that new modalities based on scientific evidence can be developed to prevent and treat tendinopathy more effectively.

References

- Ackermann PW, Finn A, Ahmed M. Sensory neuropeptidergic pattern in tendon, ligament and joint capsule: a study in the rat. *Neuroreport*. 13 1999;10:2055–2060.
- Ackermann PW, Li J, Finn A, Ahmed M, Kreicbergs A. Autonomic innervation of tendons, ligaments and joint capsules: a morphologic and quantitative study in the rat. *J Orthop Res*. 2001;19:372–378.
- Alfredson H. Chronic midportion Achilles tendinopathy: an update on research and treatment. *Clin Sports Med*. 2003;22:727–741.
- Alfredson H, Forsgren S, Thorsen K, Fahlstrom M, Johansson H, Lorentzon R. Glutamate NMDAR1 receptors localised to nerves in human Achilles tendons: implications for treatment? *Knee Surg Sports Traumatol Arthrosc*. 2001;9:123–126.
- Alfredson H, Forsgren S, Thorsen K, Lorentzon R. In vivo microdialysis and immunohistochemical analyses of tendon tissue demonstrated high amounts of free glutamate and glutamate NMDAR1 receptors, but no signs of inflammation, in Jumper's knee. *J Orthop Res*. Sep 2001;19:881–886.
- Alfredson H, Ljung BO, Thorsen K, Lorentzon R. In vivo investigation of ECRB tendons with microdialysis technique: no signs of inflammation but high amounts of glutamate in tennis elbow. *Acta Orthop Scand*. 2000;71:475–479.
- Alfredson H, Lorentzon R. Chronic Achilles tendinosis: recommendations for treatment and prevention. *Sports Med*. 2000;29:135–146.
- Alfredson H, Pietila T, Jonsson P, Lorentzon R. Heavy-load eccentric calf muscle training for the treatment of chronic Achilles tendinosis. *Am J Sports Med*. 1998;26:360–366.
- Alfredson H, Pietila T, Lorentzon R. Chronic Achilles tendinitis and calf muscle strength. *Am J Sports Med*. 1996;24:829–833.
- Alfredson H, Pietila T, Ohberg L, Lorentzon R. Achilles tendinosis and calf muscle strength: the effect of short-term immobilization after surgical treatment. *Am J Sports Med*. 1998;26:166–171.
- Alfredson H, Thorsen K, Lorentzon R. In situ microdialysis in tendon tissue: high levels of glutamate, but not prostaglandin E2 in chronic Achilles tendon pain. *Knee Surg Sports Traumatol Arthrosc*. 1999;7:378–381.
- Almekinders LC. Tendinitis and other chronic tendinopathies. *J Am Acad Orthop Surg*. 1998;6:157–164.
- Almekinders LC, Banes AJ, Ballenger CA. Effects of repetitive motion on human fibroblasts. *Med Sci Sports Exerc*. 1993;25:603–607.
- Almekinders LC, Baynes AJ, Bracey LW. An in vitro investigation into the effects of repetitive motion and nonsteroidal antiinflammatory medication on human tendon fibroblasts. *Am J Sports Med*. 1995;23:119–123.
- Almekinders LC, Temple JD. Etiology, diagnosis, and treatment of tendinitis: an analysis of the literature. *Med Sci Sports Exerc*. 1998;30:1183–1190.
- Almekinders LC, Weinhold PS, Maffulli N. Compression etiology in tendinopathy. *Clin Sports Med*. 2003;22:703–710.
- Amiel D, Woo SL, Harwood FL, Akeson WH. The effect of immobilization on collagen turnover in connective tissue: a biochemical-biomechanical correlation. *Acta Orthop Scand*. 1982;53:325–332.
- An K-N, Cooney WP, Morrey BF. The relationship between upper limb load posture and tissue loads at the elbow. In: Gordon SL, Blair SJ, Fine LJ, eds. *Repetitive Motion Disorders of the Upper Extremity*. Rosemont, IL: American Academy of Orthopaedic Surgeons; 1995:133–143.
- Apreleva M, Parsons IM, Warner JJ, Fu FH, Woo SL. Experimental investigation of reaction forces at the glenohumeral joint during active abduction. *J Shoulder Elbow Surg*. 2000;9:409–417.
- Archambault J, Tsuzaki M, Herzog W, Banes AJ. Stretch and interleukin-1beta induce matrix metalloproteinases in rabbit tendon cells in vitro. *J Orthop Res*. 2002;20:36–39.
- Archambault JM, Hart DA, Herzog W. Response of rabbit Achilles tendon to chronic repetitive loading. *Connect Tissue Res*. 2001;42:13–23.
- Arndt AN, Komi PV, Bruggemann GP, Lukkariniemi J. Individual muscle contributions to the in vivo achilles tendon force. *Clin Biomech (Bristol, Avon)*. 1998;13:532–541.
- Arnoczky SP, Tian T, Lavagnino M, Gardner K. Ex vivo static tensile loading inhibits MMP-1 expression in rat tail tendon cells through a cytoskeletally based mechanotransduction mechanism. *J Orthop Res*. 2004;22:328–333.
- Aspenberg P, Forslund C. Bone morphogenetic proteins and tendon repair. *Scand J Med Sci Sports*. 2000;10:372–375.
- Awad HA, Butler DL, Boivin GP, Smith FN, Malaviya P, Hui-bregtse B, Caplan AI. Autologous mesenchymal stem cell-mediated repair of tendon. *Tissue Eng*. 1999;5:267–277.
- Backman C, Boquist L, Friden J, Lorentzon R, Toolanen G. Chronic achilles paratenonitis with tendinosis: an experimental model in the rabbit. *J Orthop Res*. 1990;8:541–547.
- Banes AJ, Tsuzaki M, Yamamoto J, Fischer T, Brigman B, Brown T, Miller L. Mechanoreception at the cellular level: the detection, interpretation, and diversity of responses to mechanical signals. *Biochem Cell Biol*. 1995;73:349–365.
- Banes AJ, Weinhold P, Yang X, Tsuzaki M, Bynum D, Botllang M, Brown T. Gap junctions regulate responses of tendon cells ex vivo to mechanical loading. *Clin Orthop Relat Res*. 1999;367(suppl):S356–S370.
- Barbe MF, Barr AE, Gorzelany I, Amin M, Gaughan JP, Safadi FF. Chronic repetitive reaching and grasping results in decreased motor performance and widespread tissue responses in a rat model of MSD. *J Orthop Res*. 2003;21:167–176.
- Barr AE, Barbe MF, Clark BD. Work-related musculoskeletal disorders of the hand and wrist: epidemiology, pathophysiology, and sensorimotor changes. *J Orthop Sports Phys Ther*. 2004;34:610–627.

31. Benjamin M, Ralphs JR. Tendons in health and disease. *Man Ther.* 1996;1:186-191.
32. Blevins FT, Djurasovic M, Flatow EL, Vogel KG. Biology of the rotator cuff tendon. *Orthop Clin North Am.* 1997;28:1-16.
33. Brody DM. Running injuries. *Clin Symp.* 1980;32:1-36.
34. Brody DM. Running injuries. Prevention and management. *Clin Symp.* 1987;39(3):1-36.
35. Budoff JE, Nirschl RP, Ilahi OA, Rodin DM. Internal impingement in the etiology of rotator cuff tendinosis revisited. *Arthroscopy.* 2003;19:810-814.
36. Butler DL, Grood ES, Noyes FR, Zernicke RF. Biomechanics of ligaments and tendons. *Exerc Sport Sci Rev.* 1978;6:125-181.
37. Capasso G MN, Testa V. Preliminary results with peritendinous protease inhibitor injections in the management of Achilles tendinitis. *J Sports Traumatol Rel Res.* 1993;15:37-43.
38. Capasso G TV, Maffulli N. Aprotinin, corticosteroids and normosaline in the management of patellar tendinopathy in athletes: a prospective randomized study. *Sports Exerc Injury.* 1997;3:111-115.
39. Chen YJ, Wang CJ, Yang KD, Kuo YR, Huang HC, Huang YT, Sun YC, Wang FS. Extracorporeal shock waves promote healing of collagenase-induced Achilles tendinitis and increase TGF-beta1 and IGF-I expression. *J Orthop Res.* 2004;22:854-861.
40. Clancy WG Jr, Neidhart D, Brand RL. Achilles tendinitis in runners: a report of five cases. *Am J Sports Med.* 1976;4:46-57.
41. Clark JG, Kostal KM, Marino BA. Modulation of collagen production following bleomycin-induced pulmonary fibrosis in hamsters: presence of a factor in lung that increases fibroblast prostaglandin E2 and cAMP and suppresses fibroblast proliferation and collagen production. *J Biol Chem.* 25 1982;257:8098-8105.
42. Clement DB, Taunton JE, Smart GW. Achilles tendinitis and peritendinitis: etiology and treatment. *Am J Sports Med.* 1984;12:179-184.
43. Curwin S, Stanish WD. *Tendinitis: Its Etiology and Treatment.* Lexington, MA: The Collamore Press, D.C. Heath & Co; 1984.
44. Dahlgren LA, van der Meulen MC, Bertram JE, Starrak GS, Nixon AJ. Insulin-like growth factor-I improves cellular and molecular aspects of healing in a collagenase-induced model of flexor tendinitis. *J Orthop Res.* 2002;20:910-919.
45. DeJardin LM, Arnoczky SP, Ewers BJ, Haut RC, Clarke RB. Tissue-engineered rotator cuff tendon using porcine small intestine submucosa: histologic and mechanical evaluation in dogs. *Am J Sports Med.* 2001;29:175-184.
46. Devkota AC, Weinhold PS. Mechanical response of tendon subsequent to ramp loading to varying strain limits. *Clin Biomech (Bristol, Avon).* 2003;18:969-974.
47. Dow SM, Wilson AM, Goodship AE. Treatment of acute superficial digital flexor tendon injury in horses with polysulphated glycosaminoglycan. *Vet Rec.* 1996;139:413-416.
48. Elliott DH. Structure and function of mammalian tendon. *Biol Rev Camb Philos Soc.* 1965;40:392-421.
49. Finni T, Ikegawa S, Lepola V, Komi PV. Comparison of force-velocity relationships of vastus lateralis muscle in isokinetic and in stretch-shortening cycle exercises. *Acta Physiol Scand.* 2003;177:483-491.
50. Finni T, Komi PV, Lepola V. In vivo human triceps surae and quadriceps femoris muscle function in a squat jump and counter movement jump. *Eur J Appl Physiol.* 2000;83:416-426.
51. Finni T, Komi PV, Lukkariniemi J. Achilles tendon loading during walking: application of a novel optic fiber technique. *Eur J Appl Physiol Occup Physiol.* 1998;77:289-291.
52. Forslund C, Aspenberg P. Improved healing of transected rabbit Achilles tendon after a single injection of cartilage-derived morphogenetic protein-2. *Am J Sports Med.* 2003;31:555-559.
53. Fu SC, Wong YP, Chan BP, Pau HM, Cheuk YC, Lee KM, Chan KM. The roles of bone morphogenetic protein (BMP) 12 in stimulating the proliferation and matrix production of human patellar tendon fibroblasts. *Life Sci.* 2003;72:2965-2974.
54. Fujita M, Hukuda S, Doida Y. The effect of constant direct electrical current on intrinsic healing in the flexor tendon in vitro: an ultrastructural study of differing attitudes in epitenon cells and tenocytes. *J Hand Surg Br.* 1992;17:94-98.
55. Gerdesmeyer L, Wagenpfeil S, Haake M, Maier M, Loew M, Wortler K, Lampe R, Seil R, Handle G, Gassel S, Rompe JD. Extracorporeal shock wave therapy for the treatment of chronic calcifying tendonitis of the rotator cuff: a randomized controlled trial. *JAMA.* 2003;290:2573-2580.
56. Gerich TG, Kang R, Fu FH, Robbins PD, Evans CH. Gene transfer to the patellar tendon. *Knee Surg Sports Traumatol Arthrosc.* 1997; 5:118-123.
57. Gotoh M, Hamada K, Yamakawa H, Inoue A, Fukuda H. Increased substance P in subacromial bursa and shoulder pain in rotator cuff diseases. *J Orthop Res.* 1998;16:618-621.
58. Greenough CG. The effect of pulsed electromagnetic fields on flexor tendon healing in the rabbit. *J Hand Surg Br.* 1996;21:808-812.
59. Hales TR, Bernard BP. Epidemiology of work-related musculoskeletal disorders. *Orthop Clin North Am.* 1996;27:679-709.
60. Hannallah D, Peterson B, Lieberman JR, Fu FH, Huard J. Gene therapy in orthopaedic surgery. *Instr Course Lect.* 2003;52:753-768.
61. Harding DC, Brandt KD, Hillberry BM. Finger joint force minimization in pianists using optimization techniques. *J Biomech.* 1993;26:1403-1412.
62. Hart DA, Frank CB, Bray RC. Inflammatory processes in repetitive motion and overuse syndromes: potential role of neurogenic mechanisms in tendons and ligaments. In: Gordon SL, Blair SJ, Fine LJ, eds. *Repetitive Motion Disorders of the Upper Extremity.* Rosemont, IL: American Academy of Orthopaedic Surgeons; 1995:247-262.
63. Hart DA, Kydd A, Reno C. Gender and pregnancy affect neuropeptide responses of the rabbit Achilles tendon. *Clin Orthop Relat Res.* 1999;365:237-246.
64. Hsu RW, Hsu WH, Tai CL, Lee KF. Effect of shock-wave therapy on patellar tendinopathy in a rabbit model. *J Orthop Res.* 2004; 22:221-227.
65. Hubbard RP, Chun KJ. Mechanical responses of tendons to repeated extensions and wait periods. *J Biomech Eng.* 1988;110: 11-19.
66. Ito M, Kawakami Y, Ichinose Y, Fukushima S, Fukunaga T. Non-isometric behavior of fascicles during isometric contractions of a human muscle. *J Appl Physiol.* 1998;85:1230-1235.
67. Jackson BA, Schwane JA, Starcher BC. Effect of ultrasound therapy on the repair of Achilles tendon injuries in rats. *Med Sci Sports Exerc.* 1991;23:171-176.
68. James SL, Bates BT, Osternig LR. Injuries to runners. *Am J Sports Med.* 1978;6:40-50.
69. Jarvinen M, Jozsa L, Kannus P, Jarvinen TL, Kvist M, Leadbetter W. Histopathological findings in chronic tendon disorders. *Scand J Med Sci Sports.* 1997;7:86-95.
70. Jorgensen U, Ekstrand J. Significance of heel pad confinement for the shock absorption at heel strike. *Int J Sports Med.* 1988;9:468-473.
71. Jozsa L, Kannus P. Histopathological findings in spontaneous tendon ruptures. *Scand J Med Sci Sports.* 1997;7:113-118.
72. Jozsa L, Kannus P. Overuse injuries of tendons. In: Jozsa L, Kannus P, eds. *Human Tendons: Anatomy, Physiology, and Pathology.* Champaign, IL: Human Kinetics; 1997:164-253.
73. Juncosa N, West JR, Galloway MT, Boivin GP, Butler DL. In vivo forces used to develop design parameters for tissue engineered implants for rabbit patellar tendon repair. *J Biomech.* 2003;36: 483-488.
74. Kannus P, Jozsa L. Histopathological changes preceding spontaneous rupture of a tendon: a controlled study of 891 patients. *J Bone Joint Surg Am.* 1991;73:1507-1525.
75. Kannus P, Jozsa L, Natri A, Jarvinen M. Effects of training, immobilization and remobilization on tendons. *Scand J Med Sci Sports.* 1997;7:67-71.
76. Karlsson J, Kalebo P, Goksor LA, Thomee R, Sward L. Partial

- rupture of the patellar ligament. *Am J Sports Med.* 1992;20:390–395.
77. Karlsson J, Lundin O, Lossing IW, Peterson L. Partial rupture of the patellar ligament: results after operative treatment. *Am J Sports Med.* 1991;19:403–408.
 78. Kennedy JC, Willis RB. The effects of local steroid injections on tendons: a biomechanical and microscopic correlative study. *Am J Sports Med.* 1976;4:11–21.
 79. Ker RF. The implications of the adaptable fatigue quality of tendons for their construction, repair and function. *Comp Biochem Physiol A Mol Integr Physiol.* 2002;133:987–1000.
 80. Khan KM, Cook JL, Bonar F, Harcourt P, Astrom M. Histopathology of common tendinopathies: update and implications for clinical management. *Sports Med.* 1999;27:393–408.
 81. Khan KM, Cook JL, Kannus P, Maffulli N, Bonar SF. Time to abandon the “tendinitis” myth. *BMJ.* 2002;324:626–627.
 82. Khan MH, Li Z, Wang JH. Repeated exposure of tendon to prostaglandin-e2 leads to localized tendon degeneration. *Clin J Sport Med.* 2005;15:27–33.
 83. Kirkendall DT, Garrett WE. Function and biomechanics of tendons. *Scand J Med Sci Sports.* 1997;7:62–66.
 84. Kjaer M. Role of extracellular matrix in adaptation of tendon and skeletal muscle to mechanical loading. *Physiol Rev.* 2004;84:649–698.
 85. Kjaer M. The treatment of overuse injuries in sports. *Scand J Med Sci Sports.* 2001;11:195–196.
 86. Komi PV. Relevance of in vivo force measurements to human biomechanics. *J Biomech.* 1990;23(suppl 1):23–34.
 87. Korvick DL, Cummings JF, Grood ES, Holden JP, Feder SM, Butler DL. The use of an implantable force transducer to measure patellar tendon forces in goats. *J Biomech.* 1996;29:557–561.
 88. Koskinen SO, Heinemeier KM, Olesen JL, Langberg H, Kjaer M. Physical exercise can influence local levels of matrix metalloproteinases and their inhibitors in tendon-related connective tissue. *J Appl Physiol.* 2004;96:861–864.
 89. Kurtz CA, Loebig TG, Anderson DD, DeMeo PJ, Campbell PG. Insulin-like growth factor I accelerates functional recovery from Achilles tendon injury in a rat model. *Am J Sports Med.* 1999;27:363–369.
 90. Kvist M. Achilles tendon injuries in athletes. *Ann Chir Gynaecol.* 1991;80:188–201.
 91. Kvist M. Achilles tendon injuries in athletes. *Sports Med.* 1994;18:173–201.
 92. Kyrolainen H, Finni T, Avela J, Komi PV. Neuromuscular behaviour of the triceps surae muscle-tendon complex during running and jumping. *Int J Sports Med.* 2003;24:153–155.
 93. Langberg H, Rosendal L, Kjaer M. Training-induced changes in peritendinous type I collagen turnover determined by microdialysis in humans. *J Physiol.* 2001;534(pt 1):297–302.
 94. Langberg H, Skovgaard D, Asp S, Kjaer M. Time pattern of exercise-induced changes in type I collagen turnover after prolonged endurance exercise in humans. *Calcif Tissue Int.* 2000;67:41–44.
 95. Langberg H, Skovgaard D, Karamouzis M, Bulow J, Kjaer M. Metabolism and inflammatory mediators in the peritendinous space measured by microdialysis during intermittent isometric exercise in humans. *J Physiol.* 1999;515 (pt 3):919–927.
 96. Langberg H, Skovgaard D, Petersen LJ, Bulow J, Kjaer M. Type I collagen synthesis and degradation in peritendinous tissue after exercise determined by microdialysis in humans. *J Physiol.* 1999;521(pt 1):299–306.
 97. 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.
 98. Leadbetter WB. Cell-matrix response in tendon injury. *Clin Sports Med.* 1992;11:533–578.
 99. Leadbetter WB, Moar PA, Lane GJ, Lee SJ. The surgical treatment of tendinitis. Clinical rationale and biologic basis. *Clin Sports Med.* 1992;11:679–712.
 100. Lee EW, Maffulli N, Li CK, Chan KM. Pulsed magnetic and electromagnetic fields in experimental achilles tendonitis in the rat: a prospective randomized study. *Arch Phys Med Rehabil.* 1997;78:399–404.
 101. Leijnse JN. Anatomical factors predisposing to focal dystonia in the musician’s hand: principles, theoretical examples, clinical significance. *J Biomech.* 1997;30:659–669.
 102. Leijnse JN. Measuring force transfers in the deep flexors of the musician’s hand: theoretical analysis, clinical examples. *J Biomech.* 1997;30:873–882.
 103. Leppilähti J, Orava S, Karpakka J, Takala T. Overuse injuries of the Achilles tendon. *Ann Chir Gynaecol.* 1991;80:202–207.
 104. Li Z, Yang G, Khan M, Stone D, Woo SL, Wang JH. Inflammatory response of human tendon fibroblasts to cyclic mechanical stretching. *Am J Sports Med.* 2004;32:435–440.
 105. Ljung BO, Forsgren S, Friden J. Substance P and calcitonin gene-related peptide expression at the extensor carpi radialis brevis muscle origin: implications for the etiology of tennis elbow. *J Orthop Res.* 1999;17:554–559.
 106. Lorentzon R. Causes of injuries: intrinsic factors. In: Dirix A, Knuttgen HG, Tittel K, eds. *The Olympic Book of Sports Medicine.* Boston, MA: Blackwell Scientific; 1988:376–390.
 107. Lou J. In vivo gene transfer into tendon by recombinant adenovirus. *Clin Orthop Relat Res.* 2000;379(suppl):S252–S255.
 108. Lou J, Tu Y, Burns M, Silva MJ, Manske P. BMP-12 gene transfer augmentation of lacerated tendon repair. *J Orthop Res.* 2001;19:1199–1202.
 109. Maffulli N, Kader D. Tendinopathy of tendo achillis. *J Bone Joint Surg Br.* 2002;84:1–8.
 110. Maffulli N, Khan KM, Puddu G. Overuse tendon conditions: time to change a confusing terminology. *Arthroscopy.* 1998;14:840–843.
 111. Maffulli N, Testa V, Capasso G, Bifulco G, Binfield PM. Results of percutaneous longitudinal tenotomy for Achilles tendinopathy in middle- and long-distance runners. *Am J Sports Med.* 1997;25:835–840.
 112. Maffulli N, Wong J, Almekinders LC. Types and epidemiology of tendinopathy. *Clin Sports Med.* 2003;22:675–692.
 113. Mafi N, Lorentzon R, Alfredson H. Superior short-term results with eccentric calf muscle training compared to concentric training in a randomized prospective multicenter study on patients with chronic Achilles tendinosis. *Knee Surg Sports Traumatol Arthrosc.* 2001;9:42–47.
 114. Maganaris CN. Tensile properties of in vivo human tendinous tissue. *J Biomech.* 2002;35:1019–1027.
 115. Maganaris CN, Paul JP. Tensile properties of the in vivo human gastrocnemius tendon. *J Biomech.* 2002;35:1639–1646.
 116. Malaviya P, Butler DL, Korvick DL, Proch FS. In vivo tendon forces correlate with activity level and remain bounded: evidence in a rabbit flexor tendon model. *J Biomech.* 1998;31:1043–1049.
 117. Martens M, Wouters P, Burssens A, Mulier JC. Patellar tendinitis: pathology and results of treatment. *Acta Orthop Scand.* 1982;53:445–450.
 118. McNeilly CM, Banes AJ, Benjamin M, Ralphs JR. Tendon cells in vivo form a three dimensional network of cell processes linked by gap junctions. *J Anat.* 1996;189(pt 3):593–600.
 119. Messner K, Wei Y, Andersson B, Gillquist J, Rasanen T. Rat model of Achilles tendon disorder: a pilot study. *Cells Tissues Organs.* 1999;165:30–39.
 120. Molloy T, Wang Y, Murrell G. The roles of growth factors in tendon and ligament healing. *Sports Med.* 2003;33:381–394.
 121. Moore JS. Function, structure, and responses of components of the muscle-tendon unit. *Occup Med.* 1992;7:713–740.
 122. Morberg P, Jerre R, Sward L, Karlsson J. Long-term results after surgical management of partial Achilles tendon ruptures. *Scand J Med Sci Sports.* 1997;7:299–303.
 123. Muramatsu T, Muraoka T, Takeshita D, Kawakami Y, Hirano Y, Fukunaga T. Mechanical properties of tendon and aponeurosis of

- human gastrocnemius muscle in vivo. *J Appl Physiol*. 2001;90:1671–1678.
124. Mutsaers SE, Bishop JE, McGrouther G, Laurent GJ. Mechanisms of tissue repair: from wound healing to fibrosis. *Int J Biochem Cell Biol*. 1997;29:5–17.
 125. Myerson MS, McGarvey W. Disorders of the Achilles tendon insertion and Achilles tendinitis. *Instr Course Lect*. 1999;48:211–218.
 126. Nakamura N, Shino K, Natsuume T, Horibe S, Matsumoto N, Kaneda Y, Ochi T. Early biological effect of in vivo gene transfer of platelet-derived growth factor (PDGF)-B into healing patellar ligament. *Gene Ther*. 1998;5:1165–1170.
 127. Nelen G, Martens M, Burssens A. Surgical treatment of chronic Achilles tendinitis. *Am J Sports Med*. 1989;17:754–759.
 128. Nirschl RP. Elbow tendinosis/tennis elbow. *Clin Sports Med*. Oct 1992;11(4):851–870.
 129. Ohberg L, Alfredson H. Ultrasound guided sclerosis of neovessels in painful chronic Achilles tendinosis: pilot study of a new treatment. *Br J Sports Med*. 2002;36:173–175; discussion 176–177.
 130. Ozkan N, Altan L, Bingol U, Aklın S, Yurtkuran M. Investigation of the supplementary effect of GaAs laser therapy on the rehabilitation of human digital flexor tendons. *J Clin Laser Med Surg*. 2004;22:105–110.
 131. Paaavola M, Kannus P, Jarvinen TA, Khan K, Jozsa L, Jarvinen M. Achilles tendinopathy. *J Bone Joint Surg Am*. 2002;84:2062–2076.
 132. Paaavola M, Orava S, Leppilahti J, Kannus P, Jarvinen M. Chronic Achilles tendon overuse injury: complications after surgical treatment: an analysis of 432 consecutive patients. *Am J Sports Med*. 2000;28:77–82.
 133. Puddu G, Ippolito E, Postacchini F. A classification of Achilles tendon disease. *Am J Sports Med*. 1976;4:145–150.
 134. Raatikainen T, Karpakka J, Puranen J, Orava S. Operative treatment of partial rupture of the patellar ligament: a study of 138 cases. *Int J Sports Med*. 1994;15:46–49.
 135. Ralphs JR, Waggett AD, Benjamin M. Actin stress fibres and cell-cell adhesion molecules in tendons: organisation in vivo and response to mechanical loading of tendon cells in vitro. *Matrix Biol*. 2002;21:67–74.
 136. Reddy GK, Stehno-Bittel L, Enwemeka CS. Laser photostimulation of collagen production in healing rabbit Achilles tendons. *Lasers Surg Med*. 1998;22:281–287.
 137. Reilly P, Bull AMJ, Amis AA, Emory RJH. A novel technique for the quantification of tendon forces: application to the subscapularis tendon. *Trans Orthop Res Soc*. 2003;28:180.
 138. Renstrom P, Kannus P. Prevention of the sports injuries. In: Strauss RH, ed. *Sports Medicine*. Philadelphia, PA: WB Saunders; 1991:307–309.
 139. Riley G. The pathogenesis of tendinopathy: a molecular perspective. *Rheumatology (Oxford)*. 2004;43:131–142.
 140. Rivenburgh DW. Physical modalities in the treatment of tendon injuries. *Clin Sports Med*. 1992;11:645–659.
 141. Rolf C, Movin T. Etiology, histopathology, and outcome of surgery in achillodynia. *Foot Ankle Int*. 1997;18:565–569.
 142. Rompe JD, Kirkpatrick CJ, Kullmer K, Schwitalle M, Krischek O. Dose-related effects of shock waves on rabbit tendo Achillis: a sonographic and histological study. *J Bone Joint Surg Br*. 1998;80:546–552.
 143. Saltzman CL, Tearse DS. Achilles tendon injuries. *J Am Acad Orthop Surg*. 1998;6:316–325.
 144. Sandmeier R, Renstrom PA. Diagnosis and treatment of chronic tendon disorders in sports. *Scand J Med Sci Sports*. 1997;7:96–106.
 145. Schepsis AA, Leach RE. Surgical management of Achilles tendinitis. *Am J Sports Med*. 1987;15:308–315.
 146. Schuind F, Garcia-Elias M, Cooney WP 3rd, An KN. Flexor tendon forces: in vivo measurements. *J Hand Surg Am*. 1992;17:291–298.
 147. Selvanetti A CM, Puddu G. Overuse tendon injuries: basic science and classification. *Operative Tech Sports Med*. 1997:110–117.
 148. Sharma P, Maffulli N. Tendon injury and tendinopathy: healing and repair. *J Bone Joint Surg Am*. 2005;87:187–202.
 149. Sheehan FT, Drace JE. Human patellar tendon strain: a noninvasive, in vivo study. *Clin Orthop Relat Res*. 2000;370:201–207.
 150. Shrier I, Matheson GO, Kohl HW. Achilles tendonitis: are corticosteroid injections useful or harmful? *Clin J Sport Med*. 1996;6:245–250.
 151. Silver IA, Brown PN, Goodship AE, Lanyon LE, McCullagh KG, Perry GC, Williams IF. A clinical and experimental study of tendon injury, healing and treatment in the horse. *Equine Vet J Suppl*. 1983;1:1–43.
 152. Soslowsky LJ, Carpenter JE, DeBano CM, Banerji I, Moalli MR. Development and use of an animal model for investigations on rotator cuff disease. *J Shoulder Elbow Surg*. 1996;5:383–392.
 153. Soslowsky LJ, Thomopoulos S, Esmail A, Flanagan CL, Iannotti JP, Williamson JD 3rd, Carpenter JE. Rotator cuff tendinosis in an animal model: role of extrinsic and overuse factors. *Ann Biomed Eng*. 2002;30:1057–1063.
 154. Soslowsky LJ, Thomopoulos S, Tun S, Flanagan CL, Keefer CC, Mastaw J, Carpenter JE, Neer Award 1999: Overuse activity injures the supraspinatus tendon in an animal model: a histologic and biomechanical study. *J Shoulder Elbow Surg*. 2000;9:79–84.
 155. Speed CA, Richards C, Nichols D, Burnet S, Wies JT, Humphreys H, Hazleman BL. Extracorporeal shock-wave therapy for tendinitis of the rotator cuff: a double-blind, randomised, controlled trial. *J Bone Joint Surg Br*. 2002;84:509–512.
 156. Stanish WD, Rubinovich RM, Curwin S. Eccentric exercise in chronic tendinitis. *Clin Orthop Relat Res*. 1986;208:65–68.
 157. Stone D, Green C, Rao U, Aizawa H, Yamaji T, Niyibizi C, Carlin G, Woo SL. Cytokine-induced tendinitis: a preliminary study in rabbits. *J Orthop Res*. 1999;17:168–177.
 158. Sullo A, Maffulli N, Capasso G, Testa V. The effects of prolonged peritendinous administration of PGE1 to the rat Achilles tendon: a possible animal model of chronic Achilles tendinopathy. *J Orthop Sci*. 2001;6:349–357.
 159. Sundqvist H, Forsskahl B, Kvist M. A promising novel therapy for Achilles peritendinitis: double-blind comparison of glycosaminoglycan polysulfate and high-dose indomethacin. *Int J Sports Med*. 1987;8:298–303.
 160. Tasto JP, Cummings J, Medlock V, Harwood F, Hardesty R, Amiel D. The tendon treatment center: new horizons in the treatment of tendinosis. *Arthroscopy*. 2003;19(suppl 1):213–223.
 161. Thorson EP, Szabo RM. Tendinitis of the wrist and elbow. *Occup Med*. 1989;4:419–431.
 162. Tipton CM, Matthes RD, Maynard JA, Carey RA. The influence of physical activity on ligaments and tendons. *Med Sci Sports*. 1975;7:165–175.
 163. Tipton CM, Vailas AC, Matthes RD. Experimental studies on the influences of physical activity on ligaments, tendons and joints: a brief review. *Acta Med Scand Suppl*. 1986;711:157–168.
 164. Tuite MJ. MR imaging of the tendons of the foot and ankle. *Semin Musculoskelet Radiol*. 2002;6:119–131.
 165. van Griensven M, Zeichen J, Skutek M, Barkhausen T, Krettek C, Bosch U. Cyclic mechanical strain induces NO production in human patellar tendon fibroblasts: a possible role for remodelling and pathological transformation. *Exp Toxicol Pathol*. 2003;54:335–338.
 166. Varga J, Diaz-Perez A, Rosenbloom J, Jimenez SA. PGE2 causes a coordinate decrease in the steady state levels of fibronectin and types I and III procollagen mRNAs in normal human dermal fibroblasts. *Biochem Biophys Res Commun*. 1987;147:1282–1288.
 167. Veeger HE, Rozendaal LA, van der Helm FC. Load on the shoulder in low intensity wheelchair propulsion. *Clin Biomech (Bristol, Avon)*. 2002;17:211–218.
 168. Viidik A. The effect of training on the tensile strength of isolated rabbit tendons. *Scand J Plast Reconstr Surg*. 1967;1:141–147.
 169. Viidik A. Tensile strength properties of Achilles tendon systems in trained and untrained rabbits. *Acta Orthop Scand*. 1969;40:261–272.

170. Viidik A. Functional properties of collagenous tissues. *Int Rev Connect Tissue Res.* 1973;6:127–215.
171. Wada A, Kubota H, Miyanishi K, Hatanaka H, Miura H, Iwamoto Y. Comparison of postoperative early active mobilization and immobilization in vivo utilising a four-strand flexor tendon repair. *J Hand Surg Br.* 2001;26:301–306.
172. Wahrenberg H, Lindbeck L, Ekholm J. Dynamic load in the human knee joint during voluntary active impact to the lower leg. *Scand J Rehabil Med.* 1978;10:93–98.
173. Wahrenberg H, Lindbeck L, Ekholm J. Knee muscular moment, tendon tension force and EMG during a vigorous movement in man. *Scand J Rehabil Med.* 1978;10:99–106.
174. Wang CJ, Wang FS, Yang KD, Weng LH, Hsu CC, Huang CS, Yang LC. Shock wave therapy induces neovascularization at the tendon-bone junction: a study in rabbits. *J Orthop Res.* 2003;21:984–989.
175. Wang JH. Mechanobiology of tendon. *J Biomech.* Jul 4 2005.
176. Wang JH, Jia F, Yang G, Yang S, Campbell BH, Stone D, Woo SL. Cyclic mechanical stretching of human tendon fibroblasts increases the production of prostaglandin E2 and levels of cyclooxygenase expression: a novel in vitro model study. *Connect Tissue Res.* 2003;44:128–133.
177. Wang JH, Li Z, Yang G, Khan M. Repetitively stretched tendon fibroblasts produce inflammatory mediators. *Clin Orthop Relat Res.* 2004;422:243–250.
178. Weiler JM. Medical modifiers of sports injury: the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in sports soft-tissue injury. *Clin Sports Med.* 1992;11:625–644.
179. Welsh RP, Clodman J. Clinical survey of Achilles tendinitis in athletes. *Can Med Assoc J.* 1980;122:193–195.
180. West JR, Juncosa N, Galloway MT, Boivin GP, Butler DL. Characterization of in vivo Achilles tendon forces in rabbits during treadmill locomotion at varying speeds and inclinations. *J Biomech.* 2004;37:1647–1653.
181. Wiley AM. Superior humeral dislocation: a complication following decompression and debridement for rotator cuff tears. *Clin Orthop Relat Res.* 1991;263:135–141.
182. Williams JG. Achilles tendon lesions in sport. *Sports Med.* 1986;3:114–135.
183. Woo SL, Gomez MA, Amiel D, Ritter MA, Gelberman RH, Akeson WH. The effects of exercise on the biomechanical and biochemical properties of swine digital flexor tendons. *J Biomech Eng.* 1981;103:51–56.
184. Woo SL, Gomez MA, Woo YK, Akeson WH. Mechanical properties of tendons and ligaments. II. The relationships of immobilization and exercise on tissue remodeling. *Biorheology.* 1982;19:397–408.
185. Yang G, Crawford RC, Wang JH. Proliferation and collagen production of human patellar tendon fibroblasts in response to cyclic uniaxial stretching in serum-free conditions. *J Biomech.* 2004;37:1543–1550.
186. Young JS, Kumta SM, Maffulli N. Achilles tendon rupture and tendinopathy: management of complications. *Foot Ankle Clin.* 2005;10:371–382.
187. Zernicke RF, Garhammer J, Jobe FW. Human patellar-tendon rupture. *J Bone Joint Surg Am.* 1977;59:179–183.