Tendon Injury and Tendinopathy: Healing and Repair

Pankaj Sharma and Nicola Maffulli
J. Bone Joint Surg. Am. 87:187-202, 2005. doi:10.2106/JBJS.D.01850

Current Concepts Review

Tendon Injury and Tendinopathy: Healing and Repair

By Pankaj Sharma, MRCS, and Nicola Maffulli, MD, MS, PhD, FRCS(Orth)

- Tendon disorders are frequent and are responsible for substantial morbidity both in sports and in the workplace.
- *Tendinopathy,* as opposed to *tendinitis* or *tendinosis,* is the best generic descriptive term for the clinical conditions in and around tendons arising from overuse.
- Tendinopathy is a difficult problem requiring lengthy management, and patients often respond poorly to treatment.
- Preexisting degeneration has been implicated as a risk factor for acute tendon rupture.
- Several physical modalities have been developed to treat tendinopathy. There is limited and mixed high-level evidence to support the, albeit common, clinical use of these modalities.
- Further research and scientific evaluation are required before biological solutions become realistic options.

Tendons connect muscle to bone and allow transmission of forces generated by muscle to bone, resulting in joint movement. Tendon injuries produce considerable morbidity, and the disability that they cause may last for several months despite what is considered appropriate management[1]. Chronic problems caused by overuse of tendons probably account for 30% of all running-related injuries[2], and the prevalence of elbow tendinopathy in tennis players can be as high as 40%[3]. The basic cell biology of tendons is still not fully understood, and the management of tendon injury poses a considerable challenge for clinicians. This article describes the function and structure of tendons, reviews the pathophysiology of tendon injury and the phases of tendon healing, and reviews possible strategies for optimizing tendon healing and repair.

Tendon Structure

Healthy tendons are brilliant white in color and have a fibroelastic texture. Tendons demonstrate marked variation in form; they can be rounded cords, straplike bands, or flattened ribbons[4]. Within the extracellular matrix network, tenoblasts and tenocytes constitute about 90% to 95% of the cellular elements of tendons[5]. Tenoblasts are immature tendon cells. They are spindle-shaped and have numerous cytoplasmic organelles, reflecting their high metabolic activity[5]. As they mature, tenoblasts become elongated and transform into tenocytes[5]. Tenocytes have a lower nucleus-to-cytoplasm ratio than tenoblasts, with decreased metabolic activity[5]. The remaining 5% to 10% of the cellular elements of tendons consists of chondrocytes at the bone attachment and insertion sites, synovial cells of the tendon sheath, and vascular cells, including capillary endothelial cells and smooth muscle cells of arterioles. Tenocytes are active in energy generation through the aerobic Krebs cycle, anaerobic glycolysis, and the pentose phosphate shunt, and they synthesize collagen and all components of the extracellular matrix network[6-8]. With increasing age, metabolic pathways shift from aerobic to more anaerobic energy production[9,10].

The oxygen consumption of tendons and ligaments is 7.5 times lower than that of skeletal muscles[11]. The low metabolic rate and well-developed anaerobic energy-generation capacity are essential to carry loads and maintain tension for long periods, reducing the risk of ischemia and subsequent necrosis. However, a low metabolic rate results in slow healing after injury[12].

The dry mass of human tendons is approximately 30% of the total tendon mass, with water accounting for the remaining 70%. Collagen type I accounts for 65% to 80% and elastin accounts for approximately 2% of the dry mass of tendons[6,13-15]. Tenocytes and tenoblasts lie between the collagen fibers along the long axis of the tendon[16].

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 (Fig. 1)[17-19]. Soluble tropocollagen molecules form cross-links to create insoluble collagen molecules, which aggregate to form collagen fibrils. A collagen fiber is the smallest tendon unit that can be tested mechanically and is visible under light microscopy. Although collagen fibers are mainly

oriented longitudinally, fibers also run transversely and horizontally, forming spirals and plaits[20-22].

The ground substance of the extracellular matrix network surrounding the collagen and the tenocytes is composed of proteoglycans, glycosaminoglycans, glycoproteins, and several other small molecules[5]. Proteoglycans are strongly hydrophilic, enabling rapid diffusion of water-soluble molecules and the migration of cells. Adhesive glycoproteins, such as fibronectin and thrombospondin, participate in repair and regeneration processes in tendon[20,23,24]. Tenascin-C, another important component of the tendon extracellular matrix network, is abundant in the tendon body and at the osteotendinous and myotendinous junctions[25,26]. Tenascin-C contains a number of repeating fibronectin type-III domains, and, following stress-induced unfolding of these domains, it also functions as an elastic protein[26,27]. The expression of tenascin-C is regulated by mechanical strain and is upregulated in tendinopathy[25,28,29]. Tenascin-C may play a role in collagen fiber alignment and orientation[30].

The epitenon, a fine, loose connective-tissue sheath containing the vascular, lymphatic, and nerve supply to the tendon, covers the whole tendon and extends deep within it between the tertiary bundles as the endotenon. The endotenon is a thin reticular network of connective tissue investing each tendon fiber[31,32]. Superficially, the epitenon is surrounded by paratenon, a loose areolar connective tissue consisting of type-I and type-III collagen fibrils, some elastic fibrils, and an inner lining of synovial cells[3]. Synovial tendon sheaths are found in areas subjected to increased mechanical stress, such as tendons of the hands and feet, where efficient lubrication is required. Synovial sheaths consist of an outer fibrotic sheath and an inner synovial sheath, which consists of thin visceral and parietal sheets[18]. The inner synovial sheath invests the tendon body and functions as an ultrafiltration membrane to produce synovial fluid[33]. The fibrous sheath forms condensations, the pulleys, which function as fulcrums to aid tendon function[34].

At the myotendinous junction, tendinous collagen fibrils are inserted into deep recesses formed by myocyte processes, allowing the tension generated by intracellular contractile proteins of muscle fibers to be transmitted to the collagen fibrils[35-39]. This complex architecture reduces the tensile stress exerted on the tendon during muscle contraction[35]. However, the myotendinous junction still remains the weakest point of the muscle-tendon unit[35,39-42].

The osteotendinous junction is composed of four zones: a dense tendon zone, fibrocartilage, mineralized fibrocartilage, and bone[43]. The specialized structure of the osteotendinous junction prevents collagen or fiber bending, fraying, shearing, and failure[44,45].

Blood Supply

Tendons receive their blood supply from three main sources: the intrinsic systems at the myotendinous junction and osteotendinous junction, and the extrinsic system through the paratenon or the synovial sheath[46,47]. The ratio of blood supply from the intrinsic systems to that from the extrinsic system varies from tendon to tendon. For example, the central third of the rabbit Achilles tendon receives 35% of its blood supply from the extrinsic system[48,49]. At the myotendinous junction, perimysial vessels from the muscle continue between the fascicles of the tendon[25]. However, blood vessels originating from the muscle are unlikely to extend beyond the proximal third of the tendon[46]. The blood supply from the osteotendinous junction is sparse and is limited to the insertion zone of the tendon, although vessels from the extrinsic system communicate with periosteal vessels at the osteotendinous junction[5,46].

In tendons enveloped by sheaths to reduce friction,

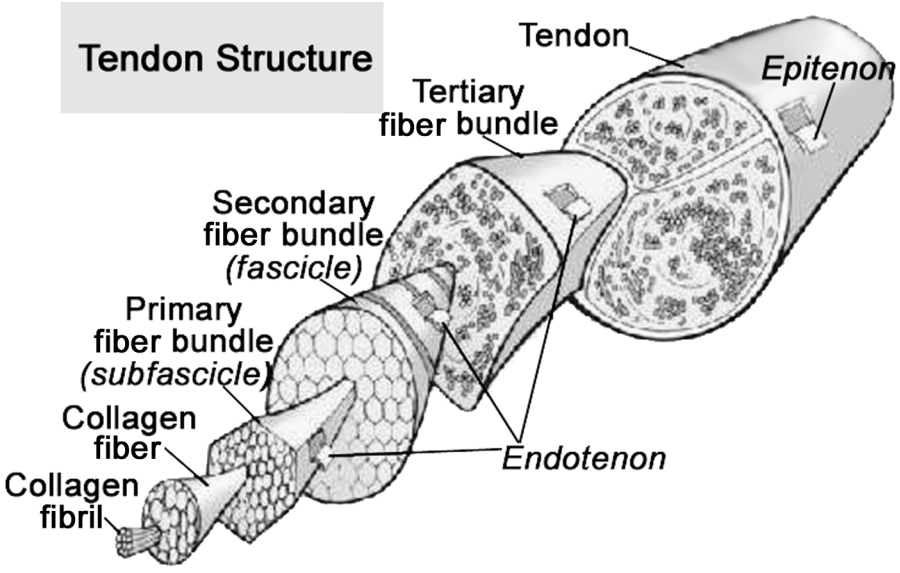

Fig. 1
Anatomy of a normal tendon.

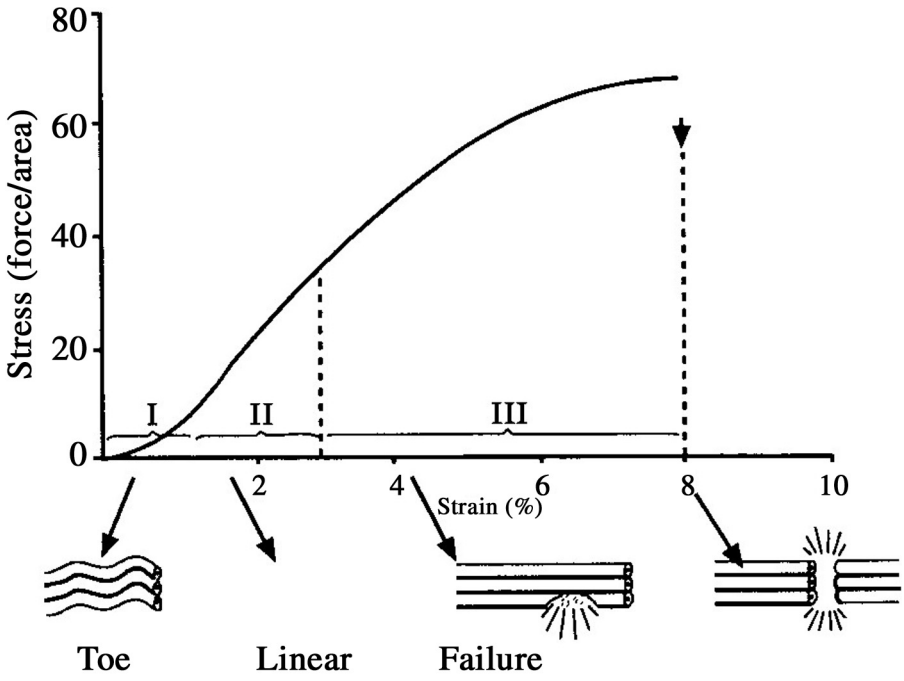

Fig. 2
Stress-strain curve demonstrating the basic physical properties of a tendon.

branches from major vessels pass through the vincula (mesotenon) to reach the visceral sheet of the synovial sheath, where they form a plexus[18] that supplies the superficial part of the tendon, while some vessels from the vincula penetrate the epitenon. These penetrating vessels course in the endotenon septa and form a connection between the peritendinous and intratendinous vascular networks.

In the absence of a synovial sheath, the paratenon provides the extrinsic component of the vasculature. Vessels entering the paratenon course transversely and branch repeatedly to form a complex vascular network[50]. Arterial branches from the paratenon penetrate the epitenon to course in the endotenon septa, where an intratendinous vascular network with abundant anastomoses is formed[5,51].

Tendon vascularity is compromised at junctional zones and sites of torsion, friction, or compression. In the Achilles tendon, angiographic injection techniques have demonstrated a zone of hypovascularity 2 to 7 cm proximal to the tendon insertion[16,52]. However, laser Doppler flowmetry has demonstrated substantially reduced blood flow near the Achilles tendon insertion, with an otherwise even blood flow throughout the tendon[53]. A similar zone of hypovascularity is present on the dorsal surface of the flexor digitorum profundus tendon subjacent to the volar plate, within 1 cm of the tendon insertion[54]. In general, tendon blood flow decreases with increasing age and mechanical loading[53].

Tendon Innervation

Tendon innervation originates from cutaneous, muscular, and peritendinous nerve trunks. At the myotendinous junction, nerve fibers cross and enter the endotenon septa. Nerve fibers form rich plexuses in the paratenon, and branches penetrate the epitenon. Most nerve fibers do not actually enter the main body of the tendon but terminate as nerve endings on its surface.

Nerve endings of myelinated fibers function as specialized mechanoreceptors to detect changes in pressure or tension. These mechanoreceptors, the Golgi tendon organs, are most numerous at the insertion of tendons into the muscle[55,56]. Golgi tendon organs are essentially a thin delicate capsule of connective tissue that encloses a group of branches of large myelinated nerve fibers. These fibers terminate with a spray of fiber endings between bundles of collagen fibers of the tendon[57,58]. Unmyelinated nerve endings act as nociceptors, and they sense and transmit pain. Both sympathetic and parasympathetic fibers are present in tendon[59].

Biomechanics

Tendons transmit force from muscle to bone and act as a buffer by absorbing external forces to limit muscle damage[60]. Tendons exhibit high mechanical strength, good flexibility, and an optimal level of elasticity to perform their unique role[16,61,62]. Tendons are viscoelastic tissues that display stress relaxation and creep[63,64].

The mechanical behavior of collagen depends on the number and types of intramolecular and intermolecular bonds[65]. A stress-strain curve helps to demonstrate the behavior of tendon (Fig. 2). At rest, collagen fibers and fibrils display a crimped configuration[66]. The initial concave portion of the curve (toe region), where the tendon is strained up to 2%, represents flattening of the crimp pattern[13,67,68]. Beyond this point, tendons deform in a linear fashion as a result of intramolecular sliding of collagen triple helices, and the fibers become more

parallel[69,70]. If the strain remains <4%, the tendon behaves in an elastic fashion and returns to its original length when unloaded[71]. Microscopic failure occurs when the strain exceeds 4%. Beyond 8% to 10% strain, macroscopic failure occurs from intrafibril damage by molecular slippage[51,67,72]. X-ray diffraction studies have demonstrated that collagen fibril elongation initially occurs as a result of molecular elongation, but as stress increases, the gap between molecules increases, eventually leading to slippage of lateral adjoining molecules[73]. After this, complete failure occurs rapidly, and the fibers recoil into a tangled bud at the ruptured end[60].

The tensile strength of tendons is related to thickness and collagen content, and a tendon with an area of 1 cm^2 is capable of bearing 500 to 1000 kg[31,74,75]. During strenuous activities such as jumping and weight-lifting, very high loads are placed on tendons[76]. Forces of 9 kN, corresponding to 12.5 times body weight, have been recorded in the human Achilles tendon during running[77-79]. Since these forces exceed the single-load ultimate tensile strength of the tendon, the rate of loading may also play an important role in tendon rupture[67,79]. Tendons are at the highest risk for rupture if tension is applied quickly and obliquely, and the highest forces are seen during eccentric muscle contraction[65,80-84].

Tendon Injury

Tendon injuries can be acute or chronic and are caused by intrinsic or extrinsic factors, either alone or in combination. In acute trauma, extrinsic factors predominate.

Tendon Rupture

An acceleration-deceleration mechanism has been reported in up to 90% of sports-related Achilles tendon ruptures[85]. Malfunction of the normal protective inhibitory pathway of the musculotendinous unit may result in injury[86]. The etiology of tendon rupture remains unclear[12]. Degenerative tendinopathy is the most common histological finding in spontaneous tendon ruptures. Arner et al. reported degenerative changes in all of their seventy-four patients with an Achilles tendon rupture, and they hypothesized that those changes were due to intrinsic abnormalities that had been present before the rupture[87]. Kannus and Jozsa found degenerative changes in 865 (97%) of 891 tendons that had spontaneously ruptured, whereas degenerative changes were seen in 149 (33%) of 445 control tendons[10]. Tendon degeneration may lead to reduced tensile strength and a predisposition to rupture. Indeed, histological evaluation of ruptured Achilles tendons has demonstrated greater degeneration than was found in tendons that were chronically painful as a result of an overuse injury[88].

Tendinopathy

Overuse injuries generally have a multifactorial origin. Interaction between intrinsic and extrinsic factors is common in chronic tendon disorders[12]. It has been claimed that intrinsic factors such as alignment and biomechanical faults play a causative role in two-thirds of Achilles tendon disorders in athletes[89,90]. In particular, hyperpronation of the foot has been linked with an increased prevalence of Achilles tendinopathy[91,92]. Excessive loading of tendons during vigorous physical training is regarded as the main pathological stimulus for degeneration[93], and there may be a greater risk of excessive loading inducing tendinopathy in the presence of intrinsic risk factors. Tendons respond to repetitive overload beyond the physiological threshold with either inflammation of their sheath or degeneration of their body, or both[94]. Different stresses induce different responses. Unless fatigue damage is actively repaired, tendons will weaken and eventually rupture[95]. The repair mechanism is probably mediated by resident tenocytes, which maintain a fine balance between extracellular matrix network production and degradation. Tendon damage may even occur from stresses within the physiological limits, as frequent cumulative microtrauma may not allow enough time for repair[93]. Microtrauma can also result from nonuniform stress within tendons, producing abnormal load concentrations and frictional forces between the fibrils and causing localized fiber damage[96].

The etiology of tendinopathy remains unclear, and many causes have been theorized[17,89]. Ischemia occurs when a tendon is under maximal tensile load. On relaxation, reperfusion occurs, generating oxygen free radicals[97,98]; this may cause tendon damage, resulting in tendinopathy[98]. Peroxiredoxin 5 is an antioxidant enzyme that protects cells against damage from such reactive oxygen species. Peroxiredoxin 5 is found in human tenocytes. Its expression is increased in tendinopathy, a finding that supports the view that oxidative stress may play a role[99]. Hypoxia alone may also result in degeneration, as tendons rely on oxidative energy metabolism to maintain cellular ATP levels[100]. During vigorous exercise, localized hypoxia may occur in tendons, with tenocyte death.

During locomotion, tendons store energy, 5% to 10% of which is converted into heat[101,102]. In the equine superficial digital flexor tendon, temperatures of up to 45°C have been recorded during galloping[103]. Although short periods at 45°C are unlikely to result in tenocyte death, repeated hyperthermic insults and prolonged hyperthermia may compromise cell viability and lead to tendon degeneration[104,105].

Excessive tenocyte apoptosis, the physiological process often referred to as "programmed cell death," has been implicated in rotator cuff tendinopathy[106]. Application of strain to tenocytes produces stress-activated protein kinases, which in turn trigger apoptosis[107,108]. Oxidative stress may play a role in inducing apoptosis, but the precise details remain to be elucidated[109]. There are more apoptotic cells in ruptured supraspinatus tendons than in normal subscapularis tendons[110]. Tendinopathic quadriceps femoris tendons exhibited a rate of spontaneous apoptosis that was 1.6 times greater than that of normal tendons[111].

In animal studies, local administration of cytokines and inflammatory prostaglandins produced a histological picture of tendinopathy[112,113]. Application of cyclic strain increases production of prostaglandin E_2 (PGE_2) in human patellar tenocytes[114], and it increases interleukin-6 (IL-6) secretion[115] and IL-1β gene expression in human flexor tenocytes[116]. Human flexor tendon cells treated with IL-1β produced increased mRNA for cycloox-

ygenase-2, matrix metalloproteinase-1 (MMP-1), MMP-3, and PGE_2[117]. IL-1β released on mechanical stretching of rabbit Achilles tendons results in increased production of MMP-3 (stromelysin-1)[118]. Hence, prolonged mechanical stimuli induce production of cytokines and inflammatory prostaglandins, which may be mediators of tendinopathy.

Ciprofloxacin also induces IL-1β-mediated MMP-3 release, and use of fluoroquinolone is associated with tendon rupture and tendinopathy[119-121]. Fluoroquinolones inhibit tenocyte metabolism, reducing cell proliferation and collagen and matrix synthesis, a mechanism that may induce tendinopathy[122,123].

MMPs, a family of proteolytic enzymes[124], are classified according to their substrate, specificity, and primary structure. They have the combined ability to degrade the components of the extracellular matrix network and to facilitate tissue remodeling[125-127]. Downregulation of MMP-3 mRNA has been reported in Achilles tendinopathy[128,129]. Alfredson et al. found, in addition to downregulation of MMP-3, upregulation of MMP-2 (gelatinase A) and vascular endothelial growth factor (VEGF) in Achilles tendinopathy compared with control samples[129]. Decreased MMP-3 and MMP-2 activity, but increased MMP-1 (collagenase-1) activity, has been reported in ruptured supraspinatus tendons[130]. However, a rabbit model of supraspinatus tears showed increased expression of MMP-2 and TIMP-1 (tissue inhibitor of metalloproteinase-1)[131].

Failure to adapt to recurrent excessive loads may result in release of cytokines by tenocytes, leading to further modulation of cell activity[132]. An increase in cytokine levels in response to repeated injury or mechanical strain may induce MMP release, with degradation of the extracellular matrix network and eventual tendinopathy. Mechanical loading studies have varied with regard to the strain protocol used, and direct comparison of their results is often difficult. The amount and frequency of application of strain may in fact determine the type and amount of cytokines released. Although an imbalance in MMP activity has been demonstrated in tendinopathic and ruptured tendons, differences in expression of the various MMPs have been reported[125-131]. A differential temporal sequence of MMP expression may occur, and MMP expression may differ between tendinopathic and ruptured tendons.

Histological Changes in Tendinopathy

The term "tendinosis" has been in use for nearly three decades to describe the pathological features of the extracellular matrix network in tendinopathy[133]. Despite that, most clinicians still use the term "tendinitis" or "tendonitis," thus implying that the fundamental problem is inflammatory. We advocate the use of the term "tendinopathy" as a generic descriptor of the clinical conditions in and around tendons arising from overuse, and we suggest that the terms "tendinosis" and "tendinitis" be used only after histopathological examination[134].

Histological examination of tendinopathy shows disordered, haphazard healing with an absence of inflammatory cells, a poor healing response, noninflammatory intratendinous collagen degeneration, fiber disorientation and thinning, hypercellularity, scattered vascular ingrowth, and increased interfibrillar glycosaminoglycans[18,135-137]. Frank inflammatory lesions and granulation tissue are infrequent and are mostly associated with tendon ruptures[138].

Various types of degeneration may be seen in tendons, but mucoid or lipoid degeneration is usually found in the Achilles tendon[18,139]. Light microscopy of a tendon with mucoid degeneration reveals large mucoid patches and vacuoles between fibers. In lipoid degeneration, abnormal intratendinous accumulation of lipid occurs, with disruption of collagen fiber structure[18,140,141]. In patellar tendinopathy, mucoid degeneration is commonly seen, although hyaline degeneration rarely occurs[142-146]. In rotator cuff tendinopathy, mucoid degeneration occurs, but fibrocartilaginous metaplasia, often accompanied by calcium deposition, is also common[147]. Amyloid deposition in supraspinatus tendons with degenerative tears has also been reported[148].

Tendinosis can be viewed as a failure of the cell matrix to adapt to a variety of stresses as a result of an imbalance between matrix degeneration and synthesis[93,132]. Macroscopically, the affected portions of the tendon are seen to have lost their normal glistening-white appearance and to have become gray-brown and amorphous. Tendon thickening, which can be diffuse, fusiform, or nodular, occurs[149]. Tendinosis is often clinically silent, and its only manifestation may be a rupture; however, it may also coexist with symptomatic paratendinopathy[98,150-152]. Mucoid degeneration, fibrosis, and vascular proliferation with a slight inflammatory infiltrate have been reported in paratendinopathy[12,153,154]. Edema and hyperemia of the paratenon are seen clinically. A fibrinous exudate accumulates within the tendon sheath, and crepitus may be felt on clinical examination[149].

In samples from 397 ruptured Achilles tendons, Kannus and Jozsa found no evidence of inflammation under light and electron microscopy[10]. Arner et al. also found no neutrophilic infiltration in Achilles tendons on the first day after rupture, and they concluded that any inflammation seen at a later stage occurred subsequent to the rupture[87]. In a recent study, immunohistochemical staining of neutrophils confirmed acute inflammation in all of sixty ruptured Achilles tendons[155]. Collagen degeneration and tenocyte necrosis may trigger an acute inflammatory response, which further weakens the tendon, predisposing it to rupture.

In summary, tendinopathy shows features of disordered healing, and inflammation is not typically seen. Although degenerative changes do not always lead to symptoms, preexisting degeneration has been implicated as a risk factor for acute tendon rupture[10,87,88]. The role played by inflammation in tendon rupture is less clear.

Pain in Tendinopathy

Classically, pain in tendinopathy was attributed to inflammation. However, chronically painful Achilles and patellar tendons show no evidence of inflammation, and many tendons with intratendinous lesions detected on magnetic resonance imaging or ultrasound are not painful[149]. Pain may originate from a combination of mechanical and biochemical factors[149].

Tendon degeneration with mechanical breakdown of collagen could theoretically explain the pain, but clinical and surgical observations have challenged this view[149]. Chemical irritants and neurotransmitters may generate pain in tendinopathy, and microdialysis sampling has revealed a twofold increase in lactate levels in tendons with tendinopathy compared with those in controls[156]. Patients with chronic Achilles tendinopathy and patellar tendinopathy showed high concentrations of the neurotransmitter glutamate, with no significant elevation of the proinflammatory prostaglandin PGE_2[157]. However, the levels of PGE_2 were consistently higher in the tendinopathic tendons than they were in controls, and it is possible that the results lacked significance because of the small sample size of the study.

Substance P functions as a neurotransmitter and neuromodulator, and it is found in small unmyelinated sensory nerve fibers[158]. A network of sensory innervation is present in tendons, and substance P has been found both in tendinopathic Achilles tendons and in medial and lateral epicondylopathy[159-162]. Sensory nerves transmit nociceptive information to the spinal cord, and increased levels of substance P correlate with pain levels in rotator cuff disease[162].

An opioid system has been demonstrated in the Achilles tendons of rats[163]. Under normal conditions, there is probably a balance between nociceptive and anti-nociceptive peptides[164,165], with alteration of this equilibrium in pathological conditions[164,165].

Tendon Healing

Studies of tendon healing predominantly have been performed on transected animal tendons or ruptured human tendons, and their relevance to healing of tendinopathic human tendons remains unclear.

Tendon healing occurs in three overlapping phases. In the initial, inflammatory phase, erythrocytes and inflammatory cells, particularly neutrophils, enter the site of injury. In the first twenty-four hours, monocytes and macrophages predominate and phagocytosis of necrotic materials occurs. Vasoactive and chemotactic factors are released with increased vascular permeability, initiation of angiogenesis, stimulation of tenocyte proliferation, and recruitment of more inflammatory cells[166]. Tenocytes gradually migrate to the wound, and type-III collagen synthesis is initiated[167].

After a few days, the proliferative phase begins. Synthesis of type-III collagen peaks during this stage and lasts for a few weeks. Water content and glycosaminoglycan concentrations remain high during this stage[167].

After approximately six weeks, the remodeling phase commences, with decreased cellularity and decreased collagen and glycosaminoglycan synthesis. The remodeling phase can be divided into a consolidation stage and a maturation stage[168]. The consolidation stage begins at about six weeks and continues for up to ten weeks. In this period, the repair tissue changes from cellular to fibrous. Tenocyte metabolism remains high during this period, and tenocytes and collagen fibers become aligned in the direction of stress[169]. A higher proportion of type-I collagen is synthesized during this stage[170]. After ten weeks, the maturation stage occurs, with gradual change of the fibrous tissue to scar-like tendon tissue over the course of one year[169,171]. During the latter half of this stage, tenocyte metabolism and tendon vascularity decline[172].

Tendon healing can occur intrinsically, by proliferation of epitenon and endotenon tenocytes, or extrinsically, by invasion of cells from the surrounding sheath and synovium[173-175]. Epitenon tenoblasts initiate the repair process through proliferation and migration[176-179]. Healing of severed tendons can be achieved by cells from the epitenon alone, without reliance on adhesions for vascularity or cellular support[180,181]. Internal tenocytes contribute to the intrinsic repair process and secrete larger and more mature collagen fibers than do epitenon cells[182]. Despite this, fibroblasts in the epitenon and tenocytes synthesize collagen during repair, and different cells probably produce different collagen types at different time-points. Initially, collagen is produced by epitenon cells, with endotenon cells synthesizing collagen later[183-187]. The relative contribution of each cell type may be influenced by the type of trauma sustained, the anatomical location, the presence of a synovial sheath, and the amount of stress induced by motion after repair has taken place[188].

Tenocyte function may vary depending on the region of origin. Cells from the tendon sheath produce less collagen and glycosaminoglycans than do epitenon and endotenon cells. However, fibroblasts from the flexor tendon sheath proliferate more rapidly[189,190]. The variation in phenotypic expression of tenocytes has not been extensively investigated, and this information may prove useful for optimizing repair strategies.

Intrinsic healing results in better biomechanics and fewer complications; in particular, a normal gliding mechanism within the tendon sheath is preserved[191]. In extrinsic healing, scar tissue results in adhesion formation, which disrupts tendon gliding[192]. Different healing patterns may predominate in particular locations; for example, extrinsic healing tends to prevail in torn rotator cuffs[193].

MMPs are important regulators of extracellular matrix network remodeling, and their levels are altered during tendon healing[126-128]. In a rat flexor tendon laceration model, the expression of MMP-9 and MMP-13 (collagenase-3) peaked between the seventh and fourteenth days after the surgery. MMP-2, MMP-3, and MMP-14 (MT1-MMP) levels increased after the surgery and remained high until the twenty-eighth day[194]. These findings suggest that MMP-9 and MMP-13 participate only in collagen degradation, whereas MMP-2, MMP-3, and MMP-14 participate both in collagen degradation and in collagen remodeling. Wounding and inflammation also provoke release of growth factors and cytokines from platelets, polymorphonuclear leukocytes, macrophages, and other inflammatory cells[195-200]. These growth factors induce neovascularization and chemotaxis of fibroblasts and tenocytes and stimulate fibroblast and tenocyte proliferation as well as synthesis of collagen[201,202].

Nitric oxide is a short-lived free radical with many biological functions: it is bactericidal, it can induce apoptosis in inflammatory cells, and it causes angiogenesis and vasodila-

tion[203-205]. Nitric oxide may play a role in several aspects of tendon healing. Nitric oxide synthase is responsible for synthesizing nitric oxide from L-arginine. Levels of nitric oxide synthase peaked after seven days and returned to baseline fourteen days after tenotomies of rat Achilles tendons[206]. In that study, inhibition of nitric oxide synthase reduced healing, resulted in a decreased cross-sectional area, and reduced failure load[206]. The authors did not identify the specific isoforms of nitric oxide synthase. More recently, the same research group demonstrated a temporal expression of the three isoforms of nitric oxide synthase[207]. The inducible isoform peaks on the fourth day, the endothelial isoform peaks on the seventh day, and the neuronal isoform peaks on the twenty-first day[207].

Interestingly, in a rat Achilles tendon rupture model, nerve fiber formation peaked between two and six weeks after the rupture, in concert with peak levels of the neuronal isoform of nitric oxide synthase[208]. These nerve fibers presumably deliver neuropeptides that act as chemical messengers and regulators, and they may play an important role in tendon healing. Substance P and calcitonin gene-related peptide (CGRP) are proinflammatory and cause vasodilation and protein extravasation[209-211]. In addition, substance P enhances cellular release of prostaglandins, histamines, and cytokines[212,213]. Levels of substance P and CGRP peak during the proliferative phase, suggesting a possible role during that phase.

Limitations of Healing

Adhesion formation after intrasynovial tendon injury poses a major clinical problem[214]. Disruption of the synovial sheath at the time of the injury or surgery allows granulation tissue and tenocytes from surrounding tissue to invade the repair site. Exogenous cells predominate over endogenous tenocytes, allowing the surrounding tissue to attach to the repair site and resulting in adhesion formation.

Despite remodeling, the biochemical and mechanical properties of healed tendon tissue never match those of intact tendon. In a study of transected sheep Achilles tendons that had spontaneously healed, the rupture force was only 56.7% of normal at twelve months[215]. One possible reason for this is the absence of mechanical loading during the period of immobilization.

Current Strategies for Tendon Healing

Physical Modalities

Many physical modalities are used in the management of tendon disorders. However, although these modalities are in routine clinical use, only a few controlled clinical trials have been performed. Most of the evidence is still pre-clinical and, at times, controversial.

Extracorporeal shock wave therapy applied to rabbit Achilles tendons, at a rate of 500 impulses of 14 kV in twenty minutes, resulted in neovascularization and an increase in the angiogenesis-related markers such as nitric oxide synthase and VEGF[216]. Extracorporeal shock wave therapy promoted healing of experimental Achilles tendinopathy in rats[217]. The authors proposed that the healing improved because of an increase in growth factor levels, as they had noted elevated levels of transforming growth factor-β1 (TGF-β1) in the early stage and persistently elevated levels of IGF-1[217]. In another study, seventy-four patients with chronic noncalcific rotator cuff tendinopathy were randomized to receive either active extracorporeal shock wave therapy (1500 pulses of 0.12 mJ/mm^2) or sham treatment monthly for three months[218]. The mean duration of symptoms was 23.3 months in both groups. All patients were assessed for pain in the shoulder, including night pain measured with a visual analogue score, and a disability index was calculated before each treatment and at one and three months after the completion of the treatment. There were no significant differences between the two groups before treatment. Both groups showed marked and sustained improvements from two months onward, but the moderate doses of extracorporeal shock wave therapy provided no added benefit compared with the sham treatment.

In a double-blind, randomized, placebo-controlled trial of 144 patients with calcific tendinopathy of the rotator cuff, patients received high-energy extracorporeal shock wave therapy, low-energy extracorporeal shock wave therapy, or a placebo (sham treatment)[219]. The two groups treated with extracorporeal shock wave therapy received the same cumulative energy dose. All patients received two treatment sessions approximately two weeks apart, followed by physical therapy. Both the high-energy and the low-energy extracorporeal shock wave therapy resulted in an improvement in the mean Constant and Murley score at six months compared with the score after the sham treatment. Also, the patients who had received the high-energy extracorporeal shock wave therapy had a higher six-month Constant and Murley score than did the patients who had received the low-energy extracorporeal shock wave therapy. Compared with the placebo, both the high-energy and the low-energy extracorporeal shock wave therapy appeared to provide a beneficial effect in terms of better shoulder function, less self-rated pain, and diminished size of calcifications. Also, the high-energy extracorporeal shock wave therapy appeared to be superior to the low-energy therapy. However, caution should be exercised when using extracorporeal shock wave therapy, as dose-dependent tendon damage, including fibrinoid necrosis, fibrosis, and inflammation, has been reported in rabbits[220].

Pulsed magnetic fields with a frequency of 17 Hz improved collagen fiber alignment in a rat Achilles tendinopathy model[221]. In another study, tenotomized rat Achilles tendons were sutured and then treated with low-intensity galvanic current for fifteen minutes a day for two weeks[222]. Biomechanical analysis revealed an increased force to breakage in the anode-stimulated group compared with controls and a cathode-stimulated group.

Direct current applied to rabbit tendons in vitro increased type-I-collagen production and decreased adhesion formation[223]. In a randomized trial, lacerated rabbit flexor tendons were repaired and then received pulsed electromagnetic field stimulation for six hours a day, starting six days after the surgery and continuing until twenty-one days after the

surgery[224]. At four weeks, no difference in adhesion formation was noted.

The effects of laser therapy on tendon healing have also been studied. Laser phototherapy increased collagen production in rabbits subjected to tenotomy and surgical repair[225]. In a placebo-controlled, double-blind, prospective study of twenty-five patients with a total of forty-one digital flexor tendon repairs, laser therapy reduced postoperative edema but provided no improvement with regard to pain relief, grip strength, or functional results compared with controls[226].

Radiofrequency coblation is a new application of bipolar radiofrequency energy used for volumetric tissue removal. Under appropriate conditions, a small vapor layer forms on the active electrode of the device. The electrical field of the energized electrode causes electrical breakdown of the vapor, producing a highly reactive plasma that is able to break down most of the bonds found in soft-tissue molecules. Radiofrequency coblation stimulates an angiogenic response in normal rabbit Achilles tendons[227]. Rapid pain relief was reported in a preliminary uncontrolled prospective, nonrandomized, single-center, single-surgeon study of twenty patients with tendinopathy of the Achilles tendon, patellar tendon, and common extensor origin[227]. Six months after the procedure, magnetic resonance imaging showed complete or near complete resolution of the tendinopathy in ten of the twenty patients.

Cytokines and Growth Factors

Increased levels of TGF-β2 have been reported in tendinopathic human Achilles tendons and in rabbit flexor tendons after injury[228,229]. TGF-β results in scar formation and fibrosis, and TGF-β1 expression is increased in patients with hypertrophic scarring and keloids following a burn[230,231]. The response to cytokines may be site-specific, and insulin-like growth factor-I (IGF-I) induces a higher rate of collagen synthesis in rabbit flexor tendons than it does in rabbit Achilles tendons[232]. The use of cytokines and growth factors to enhance tendon healing remains largely experimental and has been restricted to in vitro studies and animal models[233-249]. The clinical use of growth factors for the treatment of tendon problems has not yet been reported, to our knowledge.

Gene Therapy

Gene therapy delivers genetic material (DNA) to cells, permitting modification of cellular function, by means of viral or nonviral vectors or direct gene transfer[250,251]. Gene therapy enables the delivery of individual proteins to specific tissues and cells[252].

Several animal studies have been done to investigate the feasibility of gene transfer to tendons. For example, hemagglutinating virus of Japan (HVJ)-liposome constructs were used to deliver β-galactosidase to rat patellar tendons[253]. In vivo and ex vivo gene transfer techniques have been used as well. With these methods, sustained gene expression seems to last for about six weeks, possibly long enough for clinical applications[254,255]. Ex vivo gene transduction is possibly more efficient, but the techniques must be optimized.

Gene therapy can also alter the healing environment of tendons in animal models of tendon repair. Adenoviral transduction of focal adhesion kinase (FAK) into partially lacerated chicken flexor tendons resulted in an expected increase in adhesion formation and a twofold increase in the work required for flexion compared with the results in control groups[256]. These differences were significant ($p = 0.001$). While tendon healing was not improved in this study, the results did demonstrate that the healing environment and conditions could be manipulated.

Bone morphogenetic protein-12 (BMP-12) is the human analogue of murine GDF-7[257]. BMP-12 increases the expression of procollagen type-I and III genes in human patellar tenocytes, and it is found at sites of tendon remodeling[258]. BMP-12 increased synthesis of type-I collagen by 30% in chicken flexor tenocytes, and application of tenocytes transfected with the BMP-12 gene to a chicken flexor tendon laceration model resulted in a twofold increase in tensile strength and load to failure at four weeks[259].

Transfer of genes to tendons is feasible, and, as the healing environment can be manipulated for up to eight to ten weeks[226], this may be long enough to be clinically relevant. While the above studies were conducted in tendon transection models, delivery of substances such as platelet-derived growth factor-B (PDGF-B), BMP-12, and decorin may improve healing of tendinopathy[257-267]; additional research in this area is required.

Tissue Engineering with Mesenchymal Stem Cells

Mesenchymal stem cells are capable of undergoing differentiation into a variety of specialized mesenchymal tissues, including bone, tendon, cartilage, muscle, ligament, fat, and marrow stroma (Fig. 3)[268]. In adults, mesenchymal stem cells are prevalent in bone marrow, but they are also found in muscle, fat, and skin and around blood vessels[269]. The differentiation of mesenchymal stem cells along a particular phenotypic pathway may be controlled by a master regulatory gene, a concept formulated after the discovery of MyoD, a muscle transcription factor capable of inducing expression of a bank of muscle-specific genes[270]. However, MyoD may not be the only transcription factor responsible for myogenic differentiation; Myf5, myogenin, and MRF4 may also play a role[271]. Transcription factors that regulate adipogenic and osteogenic differentiation have also been identified, but no transcription factors regulating tenocyte differentiation have yet been identified[272-275].

Mesenchymal stem cells can be applied directly to the site of injury or can be delivered on a suitable carrier matrix, which functions as a scaffold while tissue repair takes place. In ex vivo, de novo tissue engineering with use of mesenchymal stem cells, whole body tissues are constructed in the laboratory and are subsequently implanted into patients. Tissue-engineered tendons could be used to bridge areas of tendon loss or to replace severely degenerated regions[276-279].

At present, tissue engineering is an emerging field, and many issues, such as ideal scaffold materials, optimal cell-seeding density, and optimal culture conditions, need to be established before it becomes a real option in the management of tendon disorders. Effective vascularization and innervation

of implanted tissue-engineered constructs must take place for the constructs to be viable. Vascularization allows survival of the construct. Innervation is required for proprioception and to maintain reflexes, mediated by Golgi tendon organs, to protect tendons from excessive forces[280,281].

Prevention of Adhesions

The most important factor implicated in adhesion formation is trauma[282]. Tenocytes and tenoblasts are key cells in tendon healing. The actin isoform α-smooth muscle actin has been identified in tendons and ligaments[283,284]. Tenocytes that express α-smooth muscle actin are known as myofibroblasts. There are three essential morphological elements that define myofibroblasts: stress fibers (actin microfilaments), well-developed cell-stroma attachment sites (fibronexus), and intercellular gap junctions[285]. The fibronexus is presumed to transfer tensile forces to the extracellular matrix network[286]. Myofibroblasts are thought to play a role in extracellular matrix network homeostasis in tendons and ligaments, and they may well be responsible for the formation of tendon adhesions[287].

Many attempts have been made to reduce adhesion formation by using materials acting as mechanical barriers such as polyethylene or silicone or by using pharmacological agents such as indomethacin and ibuprofen, but no simple method is widely used[288-291]. Hyaluronate is found in synovial fluid around tendon sheaths[292]. Its use decreased adhesion formation in repaired rabbit flexor tendons[293,294] but resulted in no significant differences in adhesion formation in a rat Achilles tendon model[295]. The absence of a synovial membrane around the Achilles tendon may explain this difference. A single dose of hyaluronate, at a concentration of 10 mL/mg, had no effect on rabbit tenocyte proliferation or matrix synthesis[296]. Therefore, it is unclear whether hyaluronate has any effect on myofibroblast function or just acts as a mechanical barrier. Results may vary with different doses of hyaluronate.

5-fluorouracil, an antimetabolite with anti-inflammatory properties, inhibits fibroblast proliferation, with a greater effect on synovial fibroblasts than on endotenon fibroblasts[296,297]. Lacerated chicken flexor tendons were repaired and were exposed to various doses of 5-fluorouracil for five minutes[298]. A dose of 25 mg/mL effectively preserved tendon gliding, and, at three weeks after the surgery, there was no significant difference in excursion, maximal load, or work of flexion between the repaired tendons and normal controls. Use of 50 mg/mL of 5-fluorouracil produced inferior results, suggesting that there is a therapeutic threshold beyond which 5-fluorouracil may be detrimental to tendon healing.

Despite many efforts, adhesion formation after tendon trauma remains a clinical problem, with no ideal method of prevention. With advances in the understanding of the mechanisms involved in adhesion formation, it may be possible to formulate improved strategies of prevention.

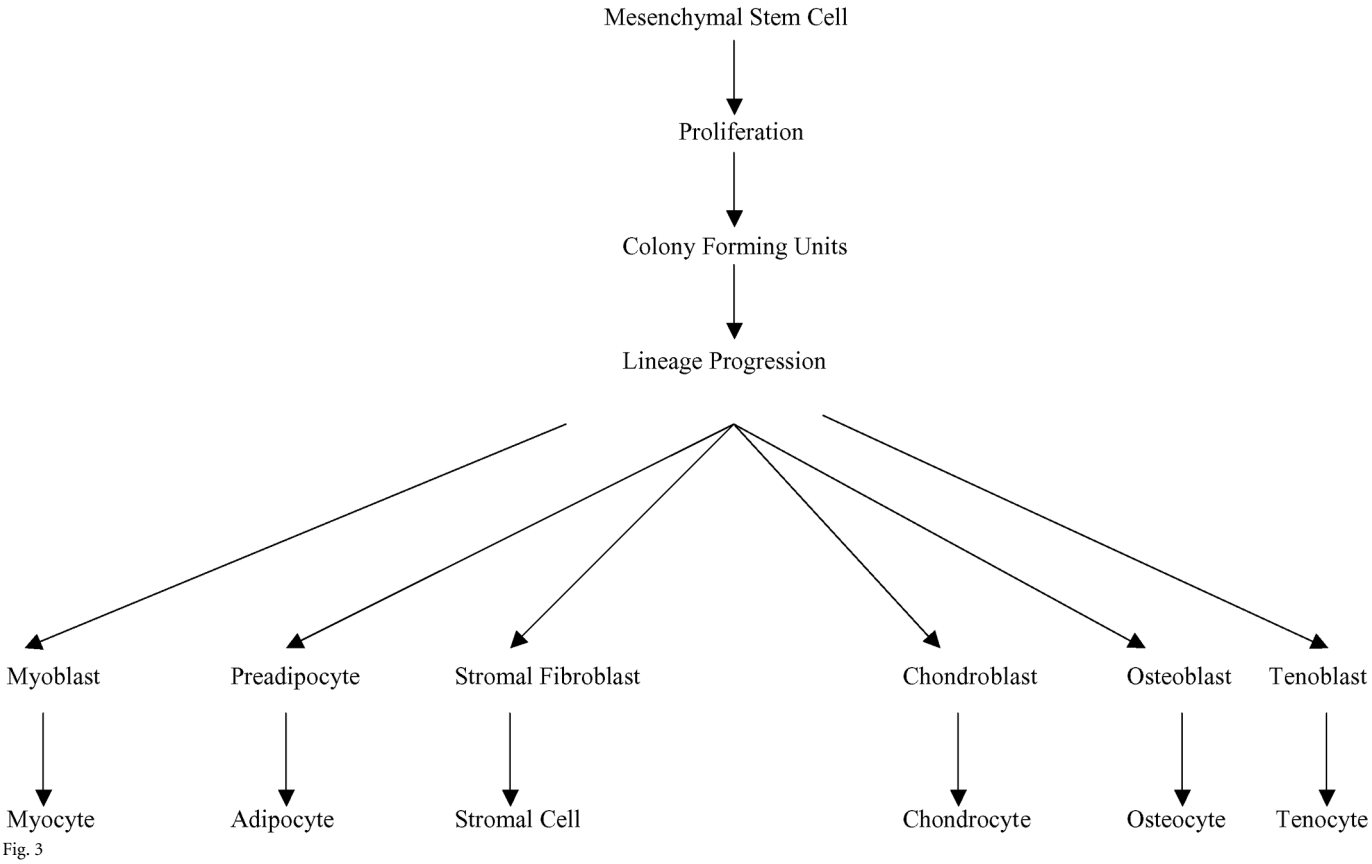

Fig. 3

Schematic representation of mesenchymal stem cell differentiation.

Mobilization and Mechanical Loading

In animal experiments, training has improved the tensile strength, elastic stiffness, weight, and cross-sectional area of tendons[299,300]. These effects can be explained by an increase in collagen and extracellular matrix network synthesis by tenocytes[300]. There are little data on the effect of exercise on human tendons, although intensively trained athletes are reported to have thicker Achilles tendons than control subjects[301]. Most of our current knowledge is therefore based on the results of animal studies. However, care must be taken when interpreting animal studies, as the results in untrained animals cannot be directly compared with those in trained animals. Also, confined animals are likely to have reduced connective-tissue mass and tendon tensile strength, and physical training may merely return these parameters to normal[302].

Prolonged immobilization following musculoskeletal injury may have detrimental effects. Collagen fascicles from stress-shielded rabbit patellar tendons displayed lower tensile strength and strain at failure than did control samples[303]. Immobilization reduces the water and proteoglycan content of tendons and increases the number of reducible collagen cross-links[304,305]. Immobilization results in tendon atrophy, but, as a result of the low metabolic rate and vascularity, these changes occur slowly[301].

After the inflammatory phase of healing, controlled stretching is likely to increase collagen synthesis and improve fiber alignment, resulting in higher tensile strength[306]. Collagen that remains unstressed during the proliferative and remodeling phases remains haphazard in organization and is weaker than stressed collagen[307]. Experimental studies have demonstrated the beneficial effects of motion and mechanical loading on tenocyte function. Repetitive motion increases DNA content and protein synthesis in human tenocytes[308]. Even fifteen minutes of cyclic biaxial mechanical strain applied to human tenocytes results in cellular proliferation[309]. Application of a cyclic load to wounded avian flexor tendons results in migration of epitenon cells into the wound[310]. In rabbit patellar tendons, application of a 4% strain provides protection against degradation by bacterial collagenase[311].

Clinical studies have shown the benefit of early mobilization following tendon repair, and several postoperative mobilization protocols have been advocated[312-316]. The precise mechanism by which cells respond to load remains to be elucidated. However, cells must respond to mechanical and chemical signals in a coordinated fashion. For example, intercellular communication by means of gap junctions is necessary to mount mitogenic and matrigenic responses in ex vivo models[317].

Overview

Tendon injuries produce substantial morbidity, and at present there are only a limited number of scientifically proven management modalities. A better understanding of tendon function and healing will allow specific treatment strategies to be developed. Many interesting techniques are being pioneered. The optimization strategies discussed in this article are currently at an early stage of development. While these emerging technologies may develop into clinical treatment options, their full impact on tendon healing needs to be critically evaluated in a scientific fashion.

Pankaj Sharma, MRCS
Nicola Maffulli, MD, MS, PhD, FRCS(Orth)
Department of Trauma and Orthopaedics, Keele University School of Medicine, Thornburrow Drive, Hartshill, Stoke-on-Trent, Staffordshire, ST4 7QB, United Kingdom. E-mail address for N. Maffulli: n.maffulli@keele.ac.uk

The authors did not receive grants or outside funding in support of their research or preparation of this manuscript. They did not receive payments or other benefits or a commitment or agreement to provide such benefits from a commercial entity. No commercial entity paid or directed, or agreed to pay or direct, any benefits to any research fund, foundation, educational institution, or other charitable or nonprofit organization with which the authors are affiliated or associated.

doi:10.2106/JBJS.D.01850

References

1. Almekinders LC, Almekinders SV. Outcome in the treatment of chronic overuse sports injuries: a retrospective study. J Orthop Sports Phys Ther. 1994;19:157-61.

2. James SL, Bates BT, Osternig LR. Injuries to runners. Am J Sports Med. 1978; 6:40-50.

3. Gruchow HW, Pelletier D. An epidemiologic study of tennis elbow. Incidence, recurrence, and effectiveness of prevention strategies. Am J Sports Med. 1979; 7:234-8.

4. Benjamin M, Ralphs J. Functional and developmental anatomy of tendons and ligaments. In: Gordon SL, Blair SJ, Fine LJ, editors. Repetitive motion disorders of the upper extremity. Rosemont, IL: American Academy of Orthopaedic Surgeons; 1995. p 185-203.

5. Kannus P, Jozsa L, Jarvinnen M. Basic science of tendons. In: Garrett WE Jr, Speer KP, Kirkendall DT, editors. Principles and practice of orthopaedic sports medicine. Philadelphia: Lippincott Williams and Wilkins; 2000. p 21-37.

6. O'Brien M. Structure and metabolism of tendons. Scand J Med Sci Sports. 1997;7:55-61.

7. Jozsa L, Balint JB, Reffy A, Demel Z. Histochemical and ultrastructural study of adult human tendon. Acta Histochem. 1979;65:250-7.

8. Kvist M, Jozsa L, Jarvinen MJ, Kvist H. Chronic Achilles paratenonitis in athletes: a histological and histochemical study. Pathology. 1987;19:1-11.

9. Kvist M, Jozsa L, Jarvinen M, Kvist H. Fine structural alterations in chronic Achilles paratenonitis in athletes. Pathol Res Pract. 1985;180:416-23.

10. Kannus P, Jozsa L. Histopathological changes preceding spontaneous rupture of a tendon. A controlled study of 891 patients. J Bone Joint Surg Am. 1991; 73:1507-25.

11. Vailas AC, Tipton CM, Laughlin HL, Tcheng TK, Matthes RD. Physical activity and hypophysectomy on the aerobic capacity of ligaments and tendons. J Appl Physiol. 1978;44:542-6.

12. Williams JG. Achilles tendon lesions in sport. Sports Med. 1986;3:114-35.

13. Hess GP, Cappiello WL, Poole RM, Hunter SC. Prevention and treatment of overuse tendon injuries. Sports Med. 1989;8:371-84.

14. Jozsa L, Lehto M, Kannus P, Kvist M, Reffy A, Vieno T, Jarvinen M, Demel S, Elek E. Fibronectin and laminin in Achilles tendon. Acta Orthop Scand. 1989; 60:469-71.

15. Tipton CM, Matthes RD, Maynard JA, Carey RA. The influence of physical activity on ligaments and tendons. Med Sci Sports. 1975;7:165-75.

16. Kirkendall DT, Garrett WE. Function and biomechanics of tendons. Scand J Med Sci Sports. 1997;7:62-6.

17. Astrom M. On the nature and etiology of chronic achilles tendinopathy [thesis]. Lund, Sweden: University of Lund; 1997.

18. Jozsa LG, Kannus P. Human tendons: anatomy, physiology, and pathology. Champaign, IL: Human Kinetics; 1997.

19. Movin T, Kristoffersen-Wiberg M, Shalabi A, Gad A, Aspelin P, Rolf C. Intratendinous alterations as imaged by ultrasound and contrast medium-enhanced magnetic resonance in chronic achillodynia. Foot Ankle Int. 1998;19:311-7.

20. Jozsa L, Kannus P, Balint JB, Reffy A. Three-dimensional ultrastructure of human tendons. Acta Anat (Basel). 1991;142:306-12.

21. Balint BJ, Jozsa L. [Investigation on the construction and spacial structure of human tendons (author's transl)]. Magy Traumatol Orthop Helyreallito Seb. 1978;21:293-9. Hungarian.

22. Hueston JT, Wilson WF. The aetiology of trigger finger explained on the basis of intratendinous architecture. Hand. 1972;4:257-60.

23. Lawler J. The structural and functional properties of thrombospondin. Blood. 1986;67:1197-209.

24. Miller RR, McDevitt CA. Thrombospondin in ligament, meniscus and intervertebral disc. Biochim Biophys Acta. 1991;1115:85-8.

25. Riley GP, Harrall RL, Cawston TE, Hazleman BL, Mackie EJ. Tenascin-C and human tendon degeneration. Am J Pathol. 1996;149:933-43.

26. Kannus P, Jozsa L, Jarvinen TA, Jarvinen TL, Kvist M, Natri A, Jarvinen M. Location and distribution of non-collagenous matrix proteins in musculoskeletal tissues of rat. Histochem J. 1998;30:799-810.

27. Oberhauser AF, Marszalek PE, Erickson HP, Fernandez JM. The molecular elasticity of the extracellular matrix protein tenascin. Nature. 1998;393:181-5.

28. Mehr D, Pardubsky PD, Martin JA, Buckwalter JA. Tenascin-C in tendon regions subjected to compression. J Orthop Res. 2000;18:537-45.

29. Jarvinen TA, Jozsa L, Kannus P, Jarvinen TL, Kvist M, Hurme T, Isola J, Kalimo H, Jarvinen M. Mechanical loading regulates tenascin-C expression in the osteotendinous junction. J Cell Sci. 1999;112:3157-66.

30. Mackie EJ, Ramsey S. Expression of tenascin in joint-associated tissues during development and postnatal growth. J Anat. 1996;188:157-65.

31. Elliott DH. Structure and function of mammalian tendon. Biol Rev Camb Philos Soc. 1965;40:392-421.

32. Kastelic J, Galeski A, Baer E. The multicomposite structure of tendon. Connect Tissue Res. 1978;6:11-23.

33. Lundborg G, Myrhage R. The vascularization and structure of the human digital tendon sheath as related to flexor tendon function. An angiographic and histological study. Scand J Plast Reconstr Surg. 1977;11:195-203.

34. Doyle JR. Anatomy of the finger flexor tendon sheath and pulley system. J Hand Surg [Am]. 1988;13:473-84.

35. Kvist M, Jozsa L, Kannus P, Isola J, Vieno T, Jarvinen M, Lehto M. Morphology and histochemistry of the myotendineal junction of the rat calf muscles. Histochemical, immunohistochemical and electron-microscopic study. Acta Anat (Basel). 1991;141:199-205.

36. Michna H. A peculiar myofibrillar pattern in the murine muscle-tendon junction. Cell Tissue Res.1983;233:227-31.

37. Trotter JA, Baca JM. A stereological comparison of the muscle-tendon junctions of fast and slow fibers in the chicken. Anat Rec. 1987;218:256-66.

38. Tidball JG, Daniel TL. Myotendinous junctions of tonic muscle cells: structure and loading. Cell Tissue Res. 1986;245:315-22.

39. Tidball JG. Myotendinous junction injury in relation to junction structure and molecular composition. Exerc Sport Sci Rev. 1991;19:419-45.

40. Nikolaou PK, Macdonald BL, Glisson RR, Seaber AV, Garrett WE Jr. Biomechanical and histological evaluation of muscle after controlled strain injury. Am J Sports Med. 1987;15:9-14.

41. Garrett WE Jr. Muscle strain injuries: clinical and basic aspects. Med Sci Sports Exerc. 1990;22:436-43.

42. Jarvinen M, Kannus P, Kvist M, Isola J, Lehto M, Jozsa L. Macromolecular composition of the myotendinous junction. Exp Mol Pathol. 1991;55:230-7.

43. Benjamin M, Ralphs JR. Fibrocartilage in tendons and ligaments—an adaptation to compressive load. J Anat. 1998;193:481-94.

44. Benjamin M, Qin S, Ralphs JR. Fibrocartilage associated with human tendons and their pulleys. J Anat. 1995;187:625-33.

45. Evans EJ, Benjamin M, Pemberton DJ. Fibrocartilage in the attachment zones of the quadriceps tendon and patellar ligament of man. J Anat. 1990;171:155-62.

46. Carr AJ, Norris SH. The blood supply of the calcaneal tendon. J Bone Joint Surg Br. 1989;71:100-1.

47. Kvist M, Hurme T, Kannus P, Jarvinen T, Maunu VM, Jozsa L, Jarvinen M. Vascular density at the myotendinous junction of the rat gastrocnemius muscle after immobilization and remobilization. Am J Sports Med. 1995;23:359-64.

48. Kvist M, Jozsa L, Jarvinen M. Vascular changes in the ruptured Achilles tendon and paratenon. Int Orthop. 1992;16:377-82.

49. Naito M, Ogata K. The blood supply of the tendon with a paratenon. An experimental study using hydrogen washout technique. Hand. 1983;15:9-14.

50. Reynolds NL, Worrell TW. Chronic Achilles peritendinitis: etiology, pathophysiology, and treatment. J Orthop Sports Phys Ther. 1991;13:171-6.

51. Field PL. Tendon fibre arrangement and blood supply. Aust NZ J Surg. 1971; 40:298-302.

52. Niculescu V, Matusz P. The clinical importance of the calcaneal tendon vasculature (tendo calcaneus). Morphol Embryol (Bucur). 1988;34:5-8.

53. Astrom M. Laser Doppler flowmetry in the assessment of tendon blood flow. Scand J Med Sci Sports. 2000;10:365-7.

54. Leversedge FJ, Ditsios K, Goldfarb CA, Silva MJ, Gelberman RH, Boyer MI. Vascular anatomy of the human flexor digitorum profundus tendon insertion. J Hand Surg [Am]. 2002;27:806-12.

55. Lephart SM, Pincivero DM, Giraldo JL, Fu FH. The role of proprioception in the management and rehabilitation of athletic injuries. Am J Sports Med. 1997;25:130-7.

56. Fitzgerald MJT. Neuroanatomy: basic and clinical. 2nd ed. Philadelphia: Balliere Tindall; 1992.

57. Brodal A. Neurological anatomy in relation to clinical medicine. 3rd ed. New York: Oxford University Press; 1981.

58. Barr ML, Kiernan JA. The human nervous system: an anatomical viewpoint. 5th ed. Philadelphia: Lippincott; 1988.

59. 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;19:372-8.

60. Best TM, Garrett WE. Basic science of soft tissue: muscle and tendon. In: DeLee JC, Drez D Jr, editors. Orthopaedic sports medicine: principles and practice. Philadelphia: WB Saunders; 1994. p 1.

61. O'Brien M. Functional anatomy and physiology of tendons. Clin Sports Med. 1992;11:505-20.

62. Oxlund H. Relationships between the biomechanical properties, composition and molecular structure of connective tissues. Connect Tissue Res. 1986; 15:65-72.

63. Carlstedt CA, Nordin M. Biomechanics of tendons and ligaments. In: Nordin M, Frankel VH, editors. Basic biomechanics of the musculoskeletal system. 2nd ed. Philadelphia: Lea and Febiger; 1989. p 59-74.

64. Viidik A. Tendons and ligaments. In: Comper W, editor. Extracellular matrix. Volume 1. Amsterdam: Harwood Academic Publishers; 1996. p 303-27.

65. Fyfe I, Stanish WD. The use of eccentric training and stretching in the treatment and prevention of tendon injuries. Clin Sports Med. 1992;11:601-24.

66. Diamant J, Keller A, Baer E, Litt M, Arridge RG. Collagen; ultrastructure and its relation to mechanical properties as a function of aging. Proc R Soc Land B Biol Sci. 1972;180:293-315.

67. Butler DL, Grood ES, Noyes FR, Zernicke RF. Biomechanics of ligaments and tendons. Exerc Sport Sci Rev. 1978;6:125-81.

68. Viidik A. Functional properties of collagenous tissues. Int Rev Connect Tissue Res. 1973;6:127-215.

69. Zernicke RF, Loitz BJ. Exercise-related adaptations in connective tissue. In: Komi PV, editor. The encyclopaedia of sports medicine. Strength and power in sport. Volume 3. Boston: Blackwell Scientific Publications; 2002. p 93-113.

70. Mosler E, Folkhard W, Knorzer E, Nemetschek-Gansler H, Nemetschek T, Koch MH. Stress-induced molecular rearrangement in tendon collagen. J Mol Biol. 1985;182:589-96.

71. Curwin S, Stanish WD. Tendinitis, its etiology and treatment. Lexington, MA: Collamore Press; 1984.

72. Kastelic J, Baer E. Deformation in tendon collagen. Symp Soc Exp Biol. 1980;34:397-435.

73. Sasaki N, Shukunami N, Matsushima N, Izumi Y. Time-resolved X-ray diffraction from tendon collagen during creep using synchrotron radiation. J Biomech. 1999;32:285-92.

74. Oakes BW, Singleton C, Haut RC. Correlation of collagen fibril morphology and tensile modulus in the repairing and normal rabbit patella tendon. Trans Orthop Res Soc. 1998;23:24.

75. Shadwick RE. Elastic energy storage in tendons: mechanical differences related to function and age. J Appl Physiol. 1990;68:1033-40.

76. Zernicke RF, Garhammer J, Jobe FW. Human patellar-tendon rupture. J Bone Joint Surg Am. 1977;59:179-83.

77. Komi PV, Salonen M, Jarvinen M, Kokko O. In vivo registration of Achilles tendon forces in man. I. Methodological development. Int J Sports Med. 1987; 8 Suppl 1:3-8.

78. Komi PV. Relevance of in vivo force measurements to human biomechanics. J Biomech. 1990;23 Suppl 1:23-34.

79. Komi PV, Fukashiro S, Jarvinen M. Biomechanical loading of Achilles tendon during normal locomotion. Clin Sports Med. 1992;11:521-31.

80. Barfred T. Experimental rupture of the Achilles tendon. Comparison of various types of experimental rupture in rats. Acta Orthop Scand. 1971;42:528-43.

81. Barfred T. Experimental rupture of the Achilles tendon. Comparison of experimental ruptures in rats of different ages and living under different conditions. Acta Orthop Scand. 1971;42:406-28.

82. Barfred T. Kinesiological comments on subcutaneous ruptures of the Achilles tendon. Acta Orthop Scand. 1971;42:397-405.

83. Komi PV. Physiological and biomechanical correlates of muscle function: effects of muscle structure and stretch-shortening cycle on force and speed. Exerc Sport Sci Rev. 1984;12:81-121.

84. Stanish WD, Curwin S, Rubinovich M. Tendinitis: the analysis and treatment for running. Clin Sports Med. 1985;4:593-609.

85. Soldatis JJ, Goodfellow DB, Wilber JH. End-to-end operative repair of Achilles tendon rupture. Am J Sports Med. 1997;25:90-5.

86. Inglis AE, Scott WN, Sculco TP, Patterson AH. Ruptures of the tendo achillis. An objective assessment of surgical and non-surgical treatment. J Bone Joint Surg Am. 1976;58:990-3.

87. Arner O, Lindholm A, Orell SR. Histologic changes in subcutaneous rupture of the Achilles tendon; a study of 74 cases. Acta Chir Scand. 1959;116: 484-90.

88. Tallon C, Maffulli N, Ewen SW. Ruptured Achilles tendons are significantly more degenerated than tendinopathic tendons. Med Sci Sports Exerc. 2001; 33:1983-90.

89. Kvist M. Achilles tendon overuse injuries: a clinical and pathophysiological study in athletes [Thesis]. Turku, Finland: University of Turku; 1991.

90. Kvist M. Achilles tendon injuries in athletes. Sports Med. 1994;18:173-201.

91. Nigg BM. The role of impact forces and foot pronation: a new paradigm. Clin J Sport Med. 2001;11:2-9.

92. Clement DB, Taunton JE, Smart GW. Achilles tendinitis and peritendinitis: etiology and treatment. Am J Sports Med. 1984;12:179-84.

93. Selvanetti A, Cipolla M, Puddu G. Overuse tendon injuries: basic science and classification. Oper Tech Sports Med. 1997;5:110-7.

94. Benazzo F, Maffulli N. An operative approach to Achilles tendinopathy. Sports Med Arthroscopy Rev. 2000;8:96-101.

95. 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.

96. Arndt AN, Komi PV, Bruggemann GP, Lukkariniemi J. Individual muscle contributions to the in vivo achilles tendon force. Clin Biomech (Bristol, Avon). 1998; 13:532-41.

97. Goodship AE, Birch HL, Wilson AM. The pathobiology and repair of tendon and ligament injury. Vet Clin North Am Equine Pract. 1994;10:323-49.

98. Bestwick CS, Maffulli N. Reactive oxygen species and tendon problems: review and hypothesis. Sports Med Arthroscopy Rev. 2000;8:6-16.

99. Wang MX, Wei A, Yuan J, Clippe A, Bernard A, Knoops B, Murrell GA. Antioxidant enzyme peroxiredoxin 5 is upregulated in degenerative human tendon. Biochem Biophys Res Commun. 2001;284:667-73.

100. Birch HL, Rutter GA, Goodship AE. Oxidative energy metabolism in equine tendon cells. Res Vet Sci. 1997;62:93-7.

101. Ker RF. Dynamic tensile properties of the plantaris tendon of sheep (Ovis aries). J Exp Biol. 1981;93:283-302.

102. Riemersma DJ, Schamhardt HC. In vitro mechanical properties of equine tendons in relation to cross-sectional area and collagen content. Res Vet Sci. 1985;39:263-70.

103. Wilson AM, Goodship AE. Exercise-induced hyperthermia as a possible mechanism for tendon degeneration. J Biomech. 1994;27:899-905.

104. Arancia G, Crateri Trovalusci P, Mariutti G, Mondovi B. Ultrastructural changes induced by hyperthermia in Chinese hamster V79 fibroblasts. Int J Hyperthermia. 1989;5:341-50.

105. Birch HL, Wilson AM, Goodship AE. The effect of exercise-induced localised hyperthermia on tendon cell survival. J Exp Biol. 1997;200:1703-8.

106. Yuan J, Wang MX, Murrell GA. Cell death and tendinopathy. Clin Sports Med. 2003;22:693-701.

107. Arnoczky SP, Tian T, Lavagnino M, Gardner K, Schuler P, Morse P. Activation of stress-activated protein kinases (SAPK) in tendon cells following cyclic strain: the effects of strain frequency, strain magnitude, and cytosolic calcium. J Orthop Res. 2002;20:947-52.

108. Skutek M, van Griensven M, Zeichen J, Brauer N, Bosch U. Cyclic mechanical stretching of human patellar tendon fibroblasts: activation of JNK and modulation of apoptosis. Knee Surg Sports Traumatol Arthrosc. 2003;11:122-9.

109. Yuan J, Murrell GA, Trickett A, Wang MX. Involvement of cytochrome c release and caspase-3 activation in the oxidative stress-induced apoptosis in human tendon fibroblasts. Biochim Biophys Acta. 2003;1641:35-41.

110. Yuan J, Murrell GA, Wei AQ, Wang MX. Apoptosis in rotator cuff tendonopathy. J Orthop Res. 2002;20:1372-9.

111. Machner A, Baier A, Wille A, Drynda S, Pap G, Drynda A, Mawrin C, Buhling F, Gay S, Neumann W, Pap T. Higher susceptibility to Fas ligand induced apoptosis and altered modulation of cell death by tumor necrosis factor-alpha in periarticular tenocytes from patients with knee joint osteoarthritis. Arthritis Res Ther. 2003;5:R253-61.

112. 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; 17:168-77.

113. 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;6:349-57.

114. 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;44:128-33.

115. Skutek M, van Griensven M, Zeichen J, Brauer N, Bosch U. Cyclic mechanical stretching enhances secretion of Interleukin 6 in human tendon fibroblasts. Knee Surg Sports Traumatol Arthrosc. 2001;9:322-6.

116. Tsuzaki M, Bynum D, Almekinders L, Yang X, Faber J, Banes AJ. ATP modulates load-inducible IL-1beta, COX 2, and MMP-3 gene expression in human tendon cells. J Cell Biochem. 2003;89:556-62.

117. Tsuzaki M, Guyton G, Garrett W, Archambault JM, Herzog W, Almekinders L, Bynum D, Yang X, Banes AJ. IL-1 beta induces COX2, MMP-1, -3 and -13, ADAMTS-4, IL-1 beta and IL-6 in human tendon cells. J Orthop Res. 2003;21:256-64.

118. 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;20:36-9.

119. Corps AN, Harrall RL, Curry VA, Fenwick SA, Hazleman BL, Riley GP. Ciprofloxacin enhances the stimulation of matrix metalloproteinase 3 expression by interleukin-1beta in human tendon-derived cells. A potential mechanism of fluoroquinolone-induced tendinopathy. Arthritis Rheum. 2002;46:3034-40.

120. Gold L, Igra H. Levofloxacin-induced tendon rupture: a case report and review of the literature. J Am Board Fam Pract. 2003;16:458-60.

121. van der Linden PD, Sturkenboom MC, Herings RM, Leufkens HG, Stricker BH. Fluoroquinolones and risk of Achilles tendon disorders: case-control study. BMJ. 2002;324:1306-7.

122. Corps AN, Curry VA, Harrall RL, Dutt D, Hazleman BL, Riley GP. Ciprofloxacin reduces the stimulation of prostaglandin E(2) output by interleukin-1beta in human tendon-derived cells. Rheumatology (Oxford). 2003;42:1306-10.

123. Williams RJ 3rd, Attia E, Wickiewicz TL, Hannafin JA. The effect of ciprofloxacin on tendon, paratenon, and capsular fibroblast metabolism. Am J Sports Med. 2000;28:364-9.

124. Murphy G, Knauper V, Atkinson S, Butler G, English W, Hutton M, Stracke J,

Clark I. Matrix metalloproteinases in arthritic disease. Arthritis Res. 2002;4 Suppl 3:S39-49.

125. Nagase H, Woessner JF. Matrix metalloproteinases. J Biol Chem. 1999;274:21491-4.

126. Vu TH, Werb Z. Matrix metalloproteinases: effectors of development and normal physiology. Genes Dev. 2000;14:2123-33.

127. Birkedal-Hansen H. Proteolytic remodeling of extracellular matrix. Curr Opin Cell Biol. 1995;7:728-35.

128. Ireland D, Harrall R, Curry V, Holloway G, Hackney R, Hazleman B, Riley G. Multiple changes in gene expression in chronic human Achilles tendinopathy. Matrix Biol. 2001;20:159-69.

129. Alfredson H, Lorentzon M, Backman S, Backman A, Lerner UH. cDNA-arrays and real-time quantitative PCR techniques in the investigation of chronic Achilles tendinosis. J Orthop Res. 2003;21:970-5.

130. Riley GP, Curry V, DeGroot J, van El B, Verzijl N, Hazleman BL, Bank RA. Matrix metalloproteinase activities and their relationship with collagen remodelling in tendon pathology. Matrix Biol. 2002;21:185-95.

131. Choi HR, Kondo S, Hirose K, Ishiguro N, Hasegawa Y, Iwata H. Expression and enzymatic activity of MMP-2 during healing process of the acute supraspinatus tendon tear in rabbits. J Orthop Res. 2002;20:927-33.

132. Leadbetter WB. Cell-matrix response in tendon injury. Clin Sports Med. 1992;11:533-78.

133. Puddu G, Ippolito E, Postacchini F. A classification of Achilles tendon disease. Am J Sports Med. 1976;4:145-50.

134. Maffulli N, Khan KM, Puddu G. Overuse tendon conditions: time to change a confusing terminology. Arthroscopy. 1998;14:840-3.

135. Khan KM, Maffulli N. Tendinopathy: an Achilles' heel for athletes and clinicians. Clin J Sport Med. 1998;8:151-4.

136. Movin T, Gad A, Reinholt FP, Rolf C. Tendon pathology in long-standing achillodynia. Biopsy findings in 40 patients. Acta Orthop Scand. 1997;68:170-5.

137. Astrom M, Rausing A. Chronic Achilles tendinopathy. A survey of surgical and histopathologic findings. Clin Orthop. 1995;316:151-64.

138. Maffulli N, Barrass V, Ewen SW. Light microscopic histology of achilles tendon ruptures. A comparison with unruptured tendons. Am J Sports Med. 2000;28:857-63.

139. 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.

140. Burry HC, Pool CJ. Central degeneration of the achilles tendon. Rheumatology Rehabilitation. 1973;12:177-81.

141. Burry HC, Pool CJ. The pathology of the painful heel. Br J Sports Med. 1971;6:9-12.

142. Colosimo AJ, Bassett FH 3rd. Jumper's knee. Diagnosis and treatment. Orthop Rev. 1990;19:139-49.

143. Fritschy D, Wallensten R. Surgical treatment of patellar tendinitis. Knee Surg Sports Traumatol Arthrosc. 1993;1:131-3.

144. Cook JL, Khan KM, Harcourt PR, Grant M, Young DA, Bonar SF. A cross sectional study of 100 athletes with jumper's knee managed conservatively and surgically. The Victorian Institute of Sport Tendon Study Group. Br J Sports Med. 1997;31:332-6.

145. 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;15:46-9.

146. Yu JS, Popp JE, Kaeding CC, Lucas J. Correlation of MR imaging and pathologic findings in athletes undergoing surgery for chronic patellar tendinitis. AJR Am J Roentgenol. 1995;165:115-8.

147. Fukuda H, Hamada K, Yamanaka K. Pathology and pathogenesis of bursal-side rotator cuff tears viewed from en bloc histologic sections. Clin Orthop. 1990;254:75-80.

148. Cole AS, Cordiner-Lawrie S, Carr AJ, Athanasou NA. Localised deposition of amyloid in tears of the rotator cuff. J Bone Joint Surg Br. 2001; 83:561-4.

149. 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.

150. Kvist M. Achilles tendon injuries in athletes. Ann Chir Gynaecol. 1991; 80:188-201.

151. Almekinders LC, Temple JD. Etiology, diagnosis, and treatment of tendonitis: an analysis of the literature. Med Sci Sports Exerc. 1998;30:1183-90.

152. Jozsa L, Kannus P. Histopathological findings in spontaneous tendon ruptures. Scand J Med Sci Sports. 1997;7:113-8.

153. Nelen G, Martens M, Burssens A. Surgical treatment of chronic Achilles tendinitis. Am J Sports Med. 1989;17:754-9.

154. Clancy WG Jr, Neidhart D, Brand RL. Achilles tendonitis in runners: a report of five cases. Am J Sports Med. 1976;4:46-57.

155. Cetti R, Junge J, Vyberg M. Spontaneous rupture of the Achilles tendon is preceded by widespread and bilateral tendon damage and ipsilateral inflammation: a clinical and histopathologic study of 60 patients. Acta Orthop Scand. 2003;74:78-84.

156. Alfredson H, Bjur D, Thorsen K, Lorentzon R, Sandstrom P. High intratendinous lactate levels in painful chronic Achilles tendinosis. An investigation using microdialysis technique. J Orthop Res. 2002;20:934-8.

157. 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;7:378-81.

158. Zubrzycka M, Janecka A. Substance P: transmitter of nociception (minireview). Endocr Regul. 2000;34:195-201.

159. Ljung BO, Forsgren S, Friden J. Sympathetic and sensory innervations are heterogeneously distributed in relation to the blood vessels at the extensor carpi radialis brevis muscle origin of man. Cells Tissues Organs. 1999;165:45-54.

160. 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;16:618-21.

161. Ackermann PW, Finn A, Ahmed M. Sensory neuropeptidergic pattern in tendon, ligament and joint capsule. A study in the rat. Neuroreport. 1999;13:2055-60.

162. Ljung BO, Alfredson H, Forsgren S. Neurokinin 1-receptors and sensory neuropeptides in tendon insertions at the medial and lateral epicondyles of the humerus. Studies on tennis elbow and medial epicondylalgia. J Orthop Res. 2004;22:321-7.

163. Ackermann PW, Spetea M, Nylander I, Ploj K, Ahmed M, Kreicbergs A. An opioid system in connective tissue: a study of achilles tendon in the rat. J Histochem Cytochem. 2001;49:1387-95.

164. Brodin E, Gazelius B, Panopoulos P, Olgart L. Morphine inhibits substance P release from peripheral sensory nerve endings. Acta Physiol Scand. 1983;1 17:567-70.

165. Yaksh TL. Substance P release from knee joint afferent terminals: modulation by opioids. Brain Res. 1988;458:319-24.

166. Murphy PG, Loitz BJ, Frank CB, Hart DA. Influence of exogenous growth factors on the synthesis and secretion of collagen types I and III by explants of normal and healing rabbit ligaments. Biochem Cell Biol. 1994;72:403-9.

167. Oakes BW. Tissue healing and repair: tendons and ligaments. In: Frontera WR, editor. Rehabilitation of sports injuries: scientific basis. Boston: Blackwell Science; 2003. p 56-98.

168. Tillman LJ, Chasan NP. Properties of dense connective tissue and wound healing. In: Hertling D, Kessler RM, editors. Management of common musculoskeletal disorders: physical therapy principles and methods. 3rd ed. Philadelphia: Lippincott; 1996. p 8-21.

169. Hooley CJ, Cohen RE. A model for the creep behaviour of tendon. Int J Biol Macromol. 1979;1:123-32.

170. Abrahamsson SO. Matrix metabolism and healing in the flexor tendon. Experimental studies on rabbit tendon. Scand J Plast Reconstr Surg Hand Surg Suppl. 1991;23:1-51.

171. Farkas LG, McCain WG, Sweeney P, Wilson W, Hurst LN, Lindsay WK. An experimental study of changes following silastic rod preparation of a new tendon sheath and subsequent tendon grafting. J Bone Joint Surg Am. 1973;55:1149-58.

172. Amiel D, Akeson W, Harwood FL, Frank CB. Stress deprivation effect on metabolic turnover of medial collateral ligament collagen. A comparison between nine- and 12-week immobilization. Clin Orthop. 1983;172:265-70.

173. Manske PR, Lesker PA. Biochemical evidence of flexor tendon participation in the repair process—an in vitro study. J Hand Surg [Br]. 1984;9:117-20.

174. Gelberman RH, Manske PR, Vande Berg JS, Lesker PA, Akeson WH. Flexor tendon repair in vitro: a comparative histologic study of the rabbit, chicken, dog, and monkey. J Orthop Res. 1984;2:39-48.

175. Potenza AD. Tendon healing within the flexor digital sheath in the dog. Am J Orthop. 1962;44:49-64.

176. Gelberman RH, Amiel D, Harwood F. Genetic expression for type I procollagen in the early stages of flexor tendon healing. J Hand Surg [Am]. 1992; 17:551-8.

177. Garner WL, McDonald JA, Kuhn C 3rd, Weeks PM. Autonomous healing of chicken flexor tendons in vitro. J Hand Surg [Am]. 1988;13:697-700.

178. Manske PR, Gelberman RH, Lesker PA. Flexor tendon healing. Hand Clin. 1985;1:25-34.

179. Mast BA, Haynes JH, Krummel TM, Diegelmann RF, Cohen IK. In vivo degradation of fetal wound hyaluronic acid results in increased fibroplasia, collagen deposition, and neovascularization. Plast Reconstr Surg. 1992;89:503-9.

180. Gelberman RH, Manske PR, Akeson WH, Woo SL, Lundborg G, Amiel D. Flexor tendon repair. J Orthop Res. 1986;4:119-28.

181. Tokita Y, Yamaya A, Yabe Y. [An experimental study on the repair and restoration of gliding function after digital flexor tendon injury. I. Repair of the sutured digital flexor tendon within digital sheath]. Nippon Seikeigeka Gakkai Zasshi. 1974;48:107-127. Japanese.

182. Fujita M, Hukuda S, Doida Y. [Experimental study of intrinsic healing of the flexor tendon: collagen synthesis of the cultured flexor tendon cells of the canine]. Nippon Seikeigeka Gakkai Zasshi. 1992;66:326-33. Japanese.

183. Ingraham JM, Hauck RM, Ehrlich HP. Is the tendon embryogenesis process resurrected during tendon healing? Plast Reconstr Surg. 2003;112:844-54.

184. Lundborg G, Rank F. Experimental studies on cellular mechanisms involved in healing of animal and human flexor tendon in synovial environment. Hand. 1980;12:3-11.

185. Lundborg G, Hansson HA, Rank F, Rydevik B. Superficial repair of severed flexor tendons in synovial environment. An experimental, ultrastructural study on cellular mechanisms. J Hand Surg [Am]. 1980;5:451-61.

186. Russell JE, Manske PR. Collagen synthesis during primate flexor tendon repair in vitro. J Orthop Res. 1990;8:13-20.

187. Becker H, Graham MF, Cohen IK, Diegelmann RF. Intrinsic tendon cell proliferation in tissue culture. J Hand Surg [Am]. 1981;6:616-9.

188. Koob TJ. Biomimetic approaches to tendon repair. Comp Biochem Physiol A Mol Integr Physiol. 2002;133:1171-92.

189. Klein MB, Pham H, Yalamanchi N, Chang J. Flexor tendon wound healing in vitro: the effect of lactate on tendon cell proliferation and collagen production. J Hand Surg [Am]. 2001;26:847-54. Erratum in: J Hand Surg [Am]. 2002; 27:740.

190. Riederer-Henderson MA, Gauger A, Olson L, Robertson C, Greenlee TK Jr. Attachment and extracellular matrix differences between tendon and synovial fibroblastic cells. In Vitro. 1983;19:127-33.

191. Koob TJ, Summers AP. Tendon—bridging the gap. Comp Biochem Physiol A Mol Integr Physiol. 2002;133:905-9.

192. Strickland JW. Flexor tendons: acute injuries. In: Green DP, Hotchkiss RN, Pedersen WC, editors. Green's operative hand surgery. 4th ed. New York: Churchill Livingstone; 1999. p 1851-97.

193. Uhthoff HK, Sarkar K. Surgical repair of rotator cuff ruptures. The importance of the subacromial bursa. J Bone Joint Surg Br. 1991;73:399-401.

194. Oshiro W, Lou J, Xing X, Tu Y, Manske PR. Flexor tendon healing in the rat: a histologic and gene expression study. J Hand Surg [Am]. 2003;28:814-23.

195. Evans CH. Cytokines and the role they play in the healing of ligaments and tendons. Sports Med. 1999;28:71-6.

196. Sciore P, Boykiw R, Hart DA. Semiquantitative reverse transcription-polymerase chain reaction analysis of mRNA for growth factors and growth factor receptors from normal and healing rabbit medial collateral ligament tissue. J Orthop Res. 1998;16:429-37.

197. Chang J, Most D, Stelnicki E, Siebert JW, Longaker MT, Hui K, Lineaweaver WC. Gene expression of transforming growth factor beta-1 in rabbit zone II flexor tendon wound healing: evidence for dual mechanisms of repair. Plast Reconstr Surg. 1997;100:937-44.

198. Chang J, Most D, Thunder R, Mehrara B, Longaker MT, Lineaweaver WC. Molecular studies in flexor tendon wound healing: the role of basic fibroblast growth factor gene expression. J Hand Surg [Am]. 1998;23:1052-8.

199. Woo SL, Hildebrand K, Watanabe N, Fenwick JA, Papageorgiou CD, Wang JH. Tissue engineering of ligament and tendon healing. Clin Orthop. 1999;367 Suppl:S312-23.

200. Natsu-ume T, Nakamura N, Shino K, Toritsuka Y, Horibe S, Ochi T. Temporal and spatial expression of transforming growth factor-beta in the healing patellar ligament of the rat. J Orthop Res. 1997;15:837-43.

201. Marui T, Niyibizi C, Georgescu HI, Cao M, Kavalkovich KW, Levine RE, Woo SL. Effect of growth factors on matrix synthesis by ligament fibroblasts. J Orthop Res. 1997;15:18-23.

202. Abrahamsson SO, Lohmander S. Differential effects of insulin-like growth factor-I on matrix and DNA synthesis in various regions and types of rabbit tendons. J Orthop Res. 1996;14:370-6.

203. Evans TJ, Buttery LD, Carpenter A, Springall DR, Polak JM, Cohen J. Cytokine-treated human neutrophils contain inducible nitric oxide synthase that produces nitration of ingested bacteria. Proc Natl Acad Sci USA. 1996;93:9553-8.

204. Richter C, Gogvadze V, Laffranchi R, Schlapbach R, Schweizer M, Suter M, Walter P, Yaffee M. Oxidants in mitochondria: from physiology to diseases. Biochim Biophys Acta. 1995;1271:67-74.

205. Ziche M, Morbidelli L, Masini E, Amerini S, Granger HJ, Maggi CA, Geppetti P, Ledda F. Nitric oxide mediates angiogenesis in vivo and endothelial cell growth and migration in vitro promoted by substance P. J Clin Invest. 1994;94:2036-44.

206. Murrell GA, Szabo C, Hannafin JA, Jang D, Dolan MM, Deng XH, Murrell DF, Warren RF. Modulation of tendon healing by nitric oxide. Inflamm Res. 1997;46:19-27.

207. Lin JH, Wang MX, Wei A, Zhu W, Diwan AD, Murrell GA. Temporal expression of nitric oxide synthase isoforms in healing Achilles tendon. J Orthop Res. 2001;19:136-42.

208. Ackermann PW. Peptidergic innervation of periarticular tissue [thesis]. Stockholm, Sweden: Karolinska Institute; 2001.

209. Nakamura-Craig M, Smith TW. Substance P and peripheral inflammatory hyperalgesia. Pain. 1989;38:91-8.

210. Maggi CA. Tachykinins and calcitonin gene-related peptide (CGRP) as cotransmitters released from peripheral endings of sensory nerves. Prog Neurobiol. 1995;45:1-98.

211. Brain SD, Williams TJ, Tippins JR, Morris HR, MacIntyre I. Calcitonin gene-related peptide is a potent vasodilator. Nature. 1985;313:54-6.

212. Vasko MR, Campbell WB, Waite KJ. Prostaglandin E2 enhances bradykinin-stimulated release of neuropeptides from rat sensory neurons in culture. J Neurosci. 1994;14:4987-97.

213. Schaible HG, Grubb BD. Afferent and spinal mechanisms of joint pain. Pain. 1993;55:5-54.

214. Manske PR. Flexor tendon healing. J Hand Surg [Br]. 1988;13:237-45.

215. Bruns J, Kampen J, Kahrs J, Plitz W. Achilles tendon rupture: experimental results on spontaneous repair in a sheep-model. Knee Surg Sports Traumatol Arthrosc. 2000;8:364-9.

216. 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;21:984-9.

217. 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;22:854-61.

218. Speed CA, Richards C, Nichols D, Burnet S, Wies JT, Humphreys H, Hazleman BL. Extracorporeal shock-wave therapy for tendonitis of the rotator cuff. A double-blind, randomised, controlled trial. J Bone Joint Surg Br. 2002;84:509-12.

219. 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;290:2573-80.

220. 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;80:546-52.

221. 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.

222. Owoeye I, Spielholz NI, Fetto J, Nelson AJ. Low-intensity pulsed galvanic current and the healing of tenotomized rat achilles tendons: preliminary report using load-to-breaking measurements. Arch Phys Med Rehabil. 1987;68:415-8.

223. 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; 17:94-8.

224. Greenough CG. The effect of pulsed electromagnetic fields on flexor tendon healing in the rabbit. J Hand Surg [Br]. 1996;21:808-12.

225. Reddy GK, Stehno-Bittel L, Enwemeka CS. Laser photostimulation of collagen production in healing rabbit Achilles tendons. Lasers Surg Med. 1998;22:281-7.

226. Ozkan N, Altan L, Bingol U, Akln 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;22:105-10.

227. 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 1:213-23.

228. Chang J, Most D, Stelnicki E, Siebert JW, Longaker MT, Hui K, Lineaweaver WC. Gene expression of transforming growth factor beta-1 in rabbit zone II flexor tendon wound healing: evidence for dual mechanisms of repair. Plast Reconstr Surg. 1997;100:937-44.

229. Banes AJ, Tsuzaki M, Hu P, Brigman B, Brown T, Almekinders L, Lawrence WT, Fischer T. PDGF-BB, IGF-I and mechanical load stimulate DNA synthesis in avian tendon fibroblasts in vitro. J Biomech. 1995;28:1505-13.

230. Ghahary A, Shen YJ, Scott PG, Gong Y, Tredget EE. Enhanced expression of mRNA for transforming growth factor-beta, type I and type III procollagen in human post-burn hypertrophic scar tissues. J Lab Clin Med. 1993;122:465-73.

231. Peltonen J, Hsiao LL, Jaakkola S, Sollberg S, Aumailley M, Timpl R, Chu ML, Uitto J. Activation of collagen gene expression in keloids: co-localization of type I and VI collagen and transforming growth factor-beta 1 mRNA. J Invest Dermatol. 1991;97:240-8.

232. Abrahamsson SO, Lohmander S. Differential effects of insulin-like growth factor-I on matrix and DNA synthesis in various regions and types of rabbit tendons. J Orthop Res. 1996;14:370-6.

233. Chang J, Thunder R, Most D, Longaker MT, Lineaweaver WC. Studies in flexor tendon wound healing: neutralizing antibody to TGF-beta1 increases postoperative range of motion. Plast Reconstr Surg. 2000;105:148-55.

234. Tsuzaki M, Brigman BE, Yamamoto J, Lawrence WT, Simmons JG, Mohapatra NK, Lund PK, Van Wyk J, Hannafin JA, Bhargava MM, Banes AJ. Insulin-like growth factor-I is expressed by avian flexor tendon cells. J Orthop Res. 2000;18:546-56.

235. Murphy DJ, Nixon AJ. Biochemical and site-specific effects of insulin-like growth factor I on intrinsic tenocyte activity in equine flexor tendons. Am J Vet Res. 1997;58:103-9.

236. 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;20:910-9.

237. Dowling BA, Dart AJ, Hodgson DR, Rose RJ, Walsh WR. Recombinant equine growth hormone does not affect the in vitro biomechanical properties of equine superficial digital flexor tendon. Vet Surg. 2002;31:325-30.

238. Ferrara N. Role of vascular endothelial growth factor in the regulation of angiogenesis. Kidney Int. 1999;56:794-814.

239. Neufeld G, Cohen T, Gengrinovitch S, Poltorak Z. Vascular endothelial growth factor (VEGF) and its receptors. FASEB J. 1999;13:9-22.

240. Pufe T, Petersen W, Tillmann B, Mentlein R. The angiogenic peptide vascular endothelial growth factor is expressed in foetal and ruptured tendons. Virchows Arch. 2001;439:579-85.

241. Bidder M, Towler DA, Gelberman RH, Boyer MI. Expression of mRNA for vascular endothelial growth factor at the repair site of healing canine flexor tendon. J Orthop Res. 2000;18:247-52.

242. Boyer MI, Watson JT, Lou J, Manske PR, Gelberman RH, Cai SR. Quantitative variation in vascular endothelial growth factor mRNA expression during early flexor tendon healing: an investigation in a canine model. J Orthop Res. 2001; 19:869-72.

243. Yang R, Thomas GR, Bunting S, Ko A, Ferrara N, Keyt B, Ross J, Jin H. Effects of vascular endothelial growth factor on hemodynamics and cardiac performance. J Cardiovasc Pharmacol. 1996;27:838-44.

244. Zhang F, Liu H, Stile F, Lei MP, Pang Y, Oswald TM, Beck J, Dorsett-Martin W, Lineaweaver WC. Effect of vascular endothelial growth factor on rat Achilles tendon healing. Plast Reconstr Surg. 2003;112:1613-9.

245. Chang SC, Hoang B, Thomas JT, Vukicevic S, Luyten FP, Ryba NJ, Kozak CA, Reddi AH, Moos M Jr. Cartilage-derived morphogenetic proteins. New members of the transforming growth factor-beta superfamily predominantly expressed in long bones during human embryonic development. J Biol Chem. 1994;269:28227-34.

246. Wolfman NM, Hattersley G, Cox K, Celeste AJ, Nelson R, Yamaji N, Dube JL, DiBlasio-Smith E, Nove J, Song JJ, Wozney JM, Rosen V. Ectopic induction of tendon and ligament in rats by growth and differentiation factors 5, 6, and 7, members of the TGF-beta gene family. J Clin Invest. 1997;100:321-30.

247. Mikic B, Schalet BJ, Clark RT, Gaschen V, Hunziker EB. GDF-5 deficiency in mice alters the ultrastructure, mechanical properties and composition of the Achilles tendon. J Orthop Res. 2001;19:365-71.

248. Forslund C, Rueger D, Aspenberg P. A comparative dose-response study of cartilage-derived morphogenetic protein (CDMP)-1, -2 and -3 for tendon healing in rats. J Orthop Res. 2003;21:617-21.

249. 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;31:555-9.

250. Nakamura N, Timmermann SA, Hart DA, Kaneda Y, Shrive NG, Shino K, Ochi T, Frank CB. A comparison of in vivo gene delivery methods for antisense therapy in ligament healing. Gene Ther. 1998;5:1455-61.

251. 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;5:1165-70.

252. Hannallah D, Peterson B, Lieberman JR, Fu FH, Huard J. Gene therapy in orthopaedic surgery. Instr Course Lect. 2003;52:753-68.

253. Nakamura N, Horibe S, Matsumoto N, Tomita T, Natsuume T, Kaneda Y, Shino K, Ochi T. Transient introduction of a foreign gene into healing rat patellar ligament. J Clin Invest. 1996;97:226-31.

254. Gerich TG, Kang R, Fu FH, Robbins PD, Evans CH. Gene transfer to the rabbit patellar tendon: potential for genetic enhancement of tendon and ligament healing. Gene Ther. 1996;3:1089-93.

255. Gerich TG, Kang R, Fu FH, Robbins PD, Evans CH. Gene transfer to the patellar tendon. Knee Surg Sports Traumatol Arthrosc. 1997;5:118-23.

256. Lou J, Kubota H, Hotokezaka S, Ludwig FJ, Manske PR. In vivo gene transfer and overexpression of focal adhesion kinase (pp125 FAK) mediated by recombinant adenovirus-induced tendon adhesion formation and epitenon cell change. J Orthop Res. 1997;15:911-8.

257. Wolfman NM, Celeste AJ, Cox K, Hattersley G, Nelson R, Yamaji N, DiBlasio-Smith E, Nove J, Song JJ, Wozney JM, Rosen V. Preliminary characterization of the biological activities of rhBMP-12. J Bone Miner Res.1995;10:S148.

258. 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;72:2965-74.

259. Lou J, Tu Y, Burns M, Silva MJ, Manske P. BMP-12 gene transfer augmentation of lacerated tendon repair. J Orthop Res. 2001;19:1199-202.

260. 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;5:1165-70.

261. Marchant JK, Hahn RA, Linsenmayer TF, Birk DE. Reduction of type V collagen using a dominant-negative strategy alters the regulation of fibrillogenesis and results in the loss of corneal-specific fibril morphology. J Cell Biol. 1996;135:1415-26.

262. Adachi E, Hayashi T. In vitro formation of hybrid fibrils of type V collagen and type I collagen. Limited growth of type I collagen into thick fibrils by type V collagen. Connect Tissue Res. 1986;14:257-66.

263. Niyibizi C, Kavalkovich K, Yamaji T, Woo SL. Type V collagen is increased during rabbit medial collateral ligament healing. Knee Surg Sports Traumatol Arthrosc. 2000;8:281-5.

264. Shimomura T, Jia F, Niyibizi C, Woo SL. Antisense oligonucleotides reduce synthesis of procollagen alpha1 (V) chain in human patellar tendon fibroblasts: potential application in healing ligaments and tendons. Connect Tissue Res. 2003;44:167-72.

265. Hart DA, Nakamura N, Marchuk L, Hiraoka H, Boorman R, Kaneda Y, Shrive NG, Frank CB. Complexity of determining cause and effect in vivo after antisense gene therapy. Clin Orthop. 2000;379 Suppl:S242-51.

266. Nakamura N, Timmermann SA, Hart DA, Kaneda Y, Shrive NG, Shino K, Ochi T, Frank CB. A comparison of in vivo gene delivery methods for antisense therapy in ligament healing. Gene Ther. 1998;5:1455-61.

267. Nakamura N, Hart DA, Boorman RS, Kaneda Y, Shrive NG, Marchuk LL, Shino K, Ochi T, Frank CB. Decorin antisense gene therapy improves functional healing of early rabbit ligament scar with enhanced collagen fibrillogenesis in vivo. J Orthop Res. 2000;18:517-23.

268. Caplan AI. The mesengenic process. Clin Plast Surg. 1994;21:429-35.

269. Caplan AI, Bruder SP. Mesenchymal stem cells: building blocks for molecular medicine in the 21st century. Trends Mol Med. 2001;7:259-64.

270. Buckingham ME. Muscle: the regulation of myogenesis. Curr Opin Genet Dev. 1994;4:745-51.

271. Dennis JE, Charbord P. Origin and differentiation of human and murine stroma. Stem Cells. 2002;20:205-14.

272. Tontonoz P, Hu E, Spiegelman BM. Stimulation of adipogenesis in fibroblasts by PPAR gamma 2, a lipid-activated transcription factor. Cell. 1994;79:1147-56. Erratum in: Cell. 1995;80:following 957.

273. Fajas L, Fruchart JC, Auwerx J. Transcriptional control of adipogenesis. Curr Opin Cell Biol. 1998;10:165-73.

274. Ducy P, Karsenty G. Genetic control of cell differentiation in the skeleton. Curr Opin Cell Biol. 1998;10:614-9.

275. Satomura K, Krebsbach P, Bianco P, Gehron Robey P. Osteogenic imprinting upstream of marrow stromal cell differentiation. J Cell Biochem. 2000;78:391-403.

276. Pelinkovic D, Lee JY, Engelhardt M, Rodosky M, Cummins J, Fu FH, Huard J. Muscle cell-mediated gene delivery to the rotator cuff. Tissue Eng. 2003;9:143-51.

277. Young RG, Butler DL, Weber W, Caplan AI, Gordon SL, Fink DJ. Use of mesenchymal stem cells in a collagen matrix for Achilles tendon repair. J Orthop Res. 1998;16:406-13.

278. Awad HA, Butler DL, Boivin GP, Smith FN, Malaviya P, Huibregtse B, Caplan AI. Autologous mesenchymal stem cell-mediated repair of tendon. Tissue Eng. 1999;5:267-77.

279. Cao Y, Liu Y, Liu W, Shan Q, Buonocore SD, Cui L. Bridging tendon defects using autologous tenocyte engineered tendon in a hen model. Plast Reconstr Surg. 2002;110:1280-9.

280. Powers SK, Howley ET. Exercise physiology: theory and application to fitness and performance. 4th ed. Boston: McGraw Hill; 2001.

281. Baechle TR, Earle R. Essentials of strength training and conditioning. Champaign, IL: Human Kinetics; 2000.

282. Jaibaji M. Advances in the biology of zone II flexor tendon healing and adhesion formation. Ann Plast Surg. 2000;45:83-92.

283. Ippolito E, Natali PG, Postacchini F, Accinni L, De Martino C. Ultrastructural and immunochemical evidence of actin in the tendon cells. Clin Orthop. 1977;126:282-4.

284. Murray MM, Spector M. Fibroblast distribution in the anteromedial bundle of the human anterior cruciate ligament: the presence of alpha-smooth muscle actin-positive cells. J Orthop Res. 1999;17:18-27.

285. Schurch W, Seemayer TA, Gabbiani G. The myofibroblast: a quarter century after its discovery. Am J Surg Pathol. 1998;22:141-7.

286. Serini G, Gabbiani G. Mechanisms of myofibroblast activity and phenotypic modulation. Exp Cell Res. 1999;250:273-83.

287. Weiler A, Unterhauser FN, Bail HJ, Huning M, Haas NP. Alpha-smooth muscle actin is expressed by fibroblastic cells of the ovine anterior cruciate ligament and its free tendon graft during remodeling. J Orthop Res. 2002;20:310-7.

288. Hunter JM, Salisbury RE. Flexor-tendon reconstruction in severely damaged hands. A two-stage procedure using a silicone-dacron reinforced gliding prosthesis prior to tendon grafting. J Bone Joint Surg Am. 1971;53:829-58.

289. Nishimura K, Nakamura RM, diZerega GS. Ibuprofen inhibition of postsurgical adhesion formation: a time and dose response biochemical evaluation in rabbits. J Surg Res. 1984;36:115-24.

290. Nishimura K, Shimanuki T, diZerega GS. Ibuprofen in the prevention of experimentally induced postoperative adhesions. Am J Med. 1984;77:102-6.

291. Szabo RM, Younger E. Effects of indomethacin on adhesion formation after repair of zone II tendon lacerations in the rabbit. J Hand Surg [Am]. 1990;15:480-3. Erratum in: J Hand Surg [Am]. 1990;15:802.

292. Hagberg L, Heinegard D, Ohlsson K. The contents of macromolecule solutes in flexor tendon sheath fluid and their relation to synovial fluid. A quantitative analysis. J Hand Surg [Br]. 1992;17:167-71.

293. Hagberg L, Gerdin B. Sodium hyaluronate as an adjunct in adhesion prevention after flexor tendon surgery in rabbits. J Hand Surg [Am]. 1992;17:935-41.

294. Tuncay I, Ozbek H, Atik B, Ozen S, Akpinar F. Effects of hyaluronic acid on postoperative adhesion of tendo calcaneus surgery: an experimental study in rats. J Foot Ankle Surg. 2002;41:104-8.

295. Wiig M, Abrahamsson SO, Lundborg G. Tendon repair—cellular activities in rabbit deep flexor tendons and surrounding synovial sheaths and the effects of hyaluronan: an experimental study in vivo and in vitro. J Hand Surg [Am]. 1997;22:818-25.

296. Khan U, Occleston NL, Khaw PT, McGrouther DA. Single exposures to 5-fluorouracil: a possible mode of targeted therapy to reduce contractile scarring in the injured tendon. Plast Reconstr Surg. 1997;99:465-71.

297. Khan U, Kakar S, Akali A, Bentley G, McGrouther DA. Modulation of the formation of adhesions during the healing of injured tendons. J Bone Joint Surg Br. 2000;82:1054-8.

298. Moran SL, Ryan CK, Orlando GS, Pratt CE, Michalko KB. Effects of 5-fluorouracil on flexor tendon repair. J Hand Surg [Am]. 2000;25:242-51.

299. Kannus P, Józsa KP, Renstrom P, Järvinen M, Kvist M, Lehto M, Oja P, Vuori I. The effects of training, immobilization and remobilization on musculoskeletal tissue. 1: training and immobilization. Scand J Med Sci Sports. 1992;2:100-18.

300. 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.

301. Maffulli N, King JB. Effects of physical activity on some components of the skeletal system. Sports Med. 1992;13:393-407.

302. Butler DL, Grood ES, Noyes FR, Zernicke RF. Biomechanics of ligaments and tendons. Exerc Sport Sci Rev. 1978;6:125-81.

303. Yamamoto E, Hayashi K, Yamamoto N. Mechanical properties of collagen fascicles from stress-shielded patellar tendons in the rabbit. Clin Biomech (Bristol, Avon). 1999;14:418-25.

304. Akeson WH, Woo SL, Amiel D, Coutts RD, Daniel D. The connective tissue response to immobility: biochemical changes in periarticular connective tissue of the immobilized rabbit knee. Clin Orthop. 1973;93:356-62.

305. Akeson WH, Amiel D, Mechanic GL, Woo SL, Harwood FL, Hamer ML. Collagen cross-linking alterations in joint contractures: changes in the reducible cross-links in periarticular connective tissue collagen after nine weeks of immobilization. Connect Tissue Res. 1977;5:15-9.

306. Kellett J. Acute soft tissue injuries—a review of the literature. Med Sci Sports Exerc. 1986;18:489-500.

307. Houglum P. Soft tissue healing and its impact on rehabilitation. J Sports Rehabil. 1992;1:19-39.

308. 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;23:119-23.

309. Zeichen J, van Griensven M, Bosch U. The proliferative response of isolated human tendon fibroblasts to cyclic biaxial mechanical strain. Am J Sports Med. 2000;28:888-92.

310. Tanaka H, Manske PR, Pruitt DL, Larson BJ. Effect of cyclic tension on lacerated flexor tendons in vitro. J Hand Surg [Am]. 1995;20:467-73.

311. Nabeshima Y, Grood ES, Sakurai A, Herman JH. Uniaxial tension inhibits tendon collagen degradation by collagenase in vitro. J Orthop Res. 1996;14:123-30.

312. Buckwalter JA. Activity vs. rest in the treatment of bone, soft tissue and joint injuries. Iowa Orthop J. 1995;15:29-42.

313. Buckwalter JA. Effects of early motion on healing of musculoskeletal tissues. Hand Clin. 1996;12:13-24.

314. Chow JA, Thomes LJ, Dovelle S, Monsivais J, Milnor WH, Jackson JP. Controlled motion rehabilitation after flexor tendon repair and grafting. A multi-centre study. J Bone Joint Surg Br. 1988;70:591-5.

315. Cullen KW, Tolhurst P, Lang D, Page RE. Flexor tendon repair in zone 2 followed by controlled active mobilisation. J Hand Surg [Br]. 1989;14:392-5.

316. Elliot D, Moiemen NS, Flemming AF, Harris SB, Foster AJ. The rupture rate of acute flexor tendon repairs mobilized by the controlled active motion regimen. J Hand Surg [Br]. 1994;19:607-12.

317. Banes AJ, Horesovsky G, Larson C, Tsuzaki M, Judex S, Archambault J, Zernicke R, Herzog W, Kelley S, Miller L. Mechanical load stimulates expression of novel genes in vivo and in vitro in avian flexor tendon cells. Osteoarthritis Cartilage. 1999;7:141-53.