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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 management¹. Chronic problems caused by overuse of tendons probably account for 30% of all running-related injuries², 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 ribbons⁴. Within the extracellular matrix network, tenoblasts and tenocytes constitute about 90% to 95% of the cellular elements of tendons⁵. Tenoblasts are immature tendon cells. They are spindle-shaped and have numerous cytoplasmic organelles, reflecting their **high metabolic activity**⁷. As they mature, tenoblasts become elongated and transform into tenocytes⁵. Tenocytes have a lower nucleus-to-cytoplasm ratio than tenoblasts, with decreased metabolic activity⁷. 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 network⁶⁻⁸. **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 muscles¹¹. **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 tendon¹⁶.

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 plaits²⁰⁻²².

The ground substance of the extracellular matrix network surrounding the collagen and the tenocytes is composed of proteoglycans, glycosaminoglycans, glycoproteins, and several other small molecules⁵. 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 orientation³⁰.

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 cells⁹. 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 sheets¹⁸. The inner synovial sheath invests the tendon body and functions as an ultrafiltration membrane to

produce synovial fluid³³. The fibrous sheath forms condensations, the pulleys, which function as fulcrums to aid tendon function³⁴.

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 fibrils³⁵⁻³⁹. This complex architecture reduces the tensile stress exerted on the tendon during muscle contraction³⁵. 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 bone⁴³. 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 tendon²⁵. However, blood vessels originating from the muscle are unlikely to extend beyond the proximal third of the tendon⁴⁶. 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,

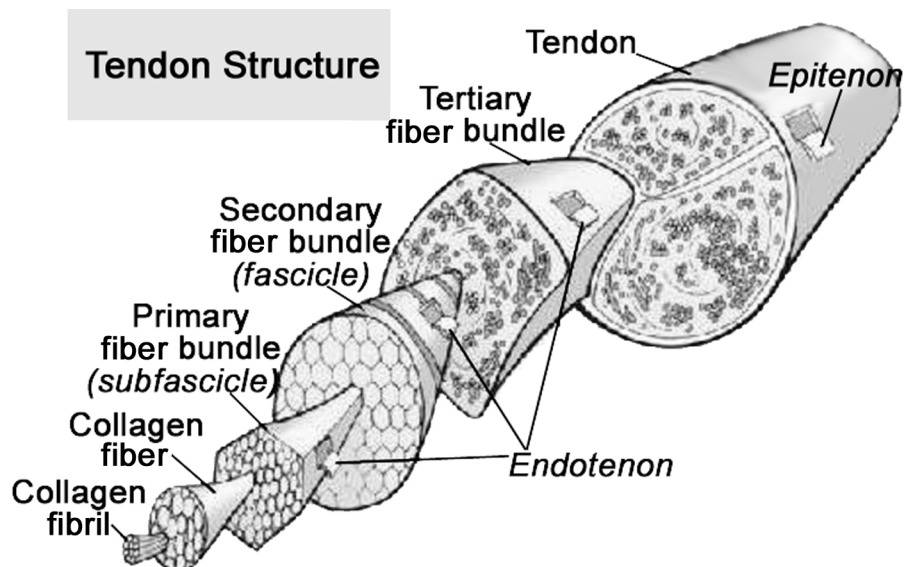


Fig. 1
Anatomy of a normal tendon.

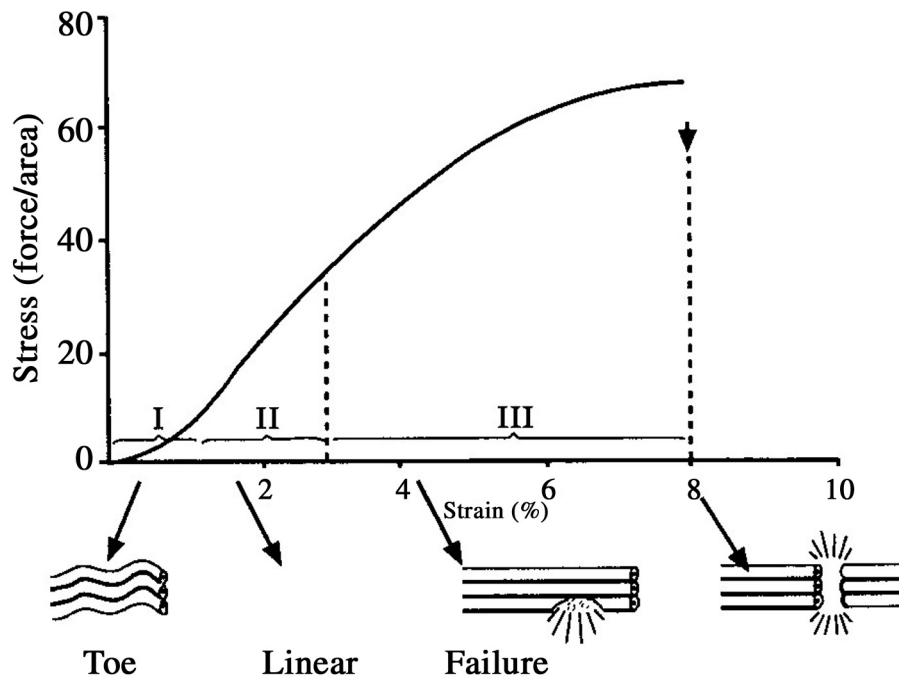


Fig. 2
Stress-strain curve demonstrating the basic physical properties of a tendon.

branches from major vessels pass through the vincula (mesotenon) to reach the visceral sheet of the synovial sheath, where they form a plexus¹⁸ 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 network⁵⁰. Arterial branches from the paratenon penetrate the epitenon to course in the endotenon septa, where an intratendinous vascular network with abundant anastomoses is formed^{55,51}.

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^{46,52}. However, laser Doppler flowmetry has demonstrated substantially reduced blood flow near the Achilles tendon insertion, with an otherwise even blood flow throughout the tendon⁵³. 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 insertion⁵⁴. In general, tendon blood flow decreases with increasing age and mechanical loading⁵³.

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 tendon⁵⁹.

Biomechanics

Tendons transmit force from muscle to bone and act as a buffer by absorbing external forces to limit muscle damage⁶⁰. 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 bonds⁶⁵. A stress-strain curve helps to demonstrate the behavior of tendon (Fig. 2). At rest, collagen fibers and fibrils display a crimped configuration⁶⁶. 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 unloaded⁷¹. Microscopic failure occurs when the strain exceeds 4%. Beyond 8% to 10% strain, macroscopic failure occurs from intrafibril damage by molecular slippage^{61,67,72}. 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 molecules⁷³. After this, complete failure occurs rapidly, and the fibers recoil into a tangled bud at the ruptured end⁶⁰.

The tensile strength of tendons is related to thickness and collagen content, and a tendon with an area of 1 cm² 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 tendons⁷⁶. Forces of 9 kN, corresponding to 12.5 times body weight, have been recorded in the human Achilles tendon during running⁷⁷⁻⁷⁹. 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 ruptures⁸⁵. Malfunction of the normal protective inhibitory pathway of the musculotendinous unit may result in injury⁸⁶. The etiology of tendon rupture remains unclear¹². 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 rupture⁸⁷. Kanus 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 tendons¹⁰. 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 injury⁸⁸.

Tendinopathy

Overuse injuries generally have a multifactorial origin. Interaction between intrinsic and extrinsic factors is common in chronic tendon disorders¹². 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 degeneration⁹³, 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 both⁹⁴. Different stresses induce different responses. Unless fatigue damage is actively repaired, tendons will weaken and eventually rupture⁹⁵. 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 repair⁹³. Microtrauma can also result from nonuniform stress within tendons, producing abnormal load concentrations and frictional forces between the fibrils and causing localized fiber damage⁹⁶.

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 tendinopathy⁹⁸. 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 role⁹⁹. Hypoxia alone may also result in degeneration, as tendons rely on oxidative energy metabolism to maintain cellular ATP levels¹⁰⁰. 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 galloping¹⁰³. 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 tendinopathy¹⁰⁶. 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 elucidated¹⁰⁹. There are more apoptotic cells in ruptured supraspinatus tendons than in normal subscapularis tendons¹¹⁰. Tendinopathic quadriceps femoris tendons exhibited a rate of spontaneous apoptosis that was 1.6 times greater than that of normal tendons¹¹¹.

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 E₂ (PGE₂) in human patellar tenocytes¹¹⁴, and it increases interleukin-6 (IL-6) secretion¹¹⁵ and IL-1 β gene expression in human flexor tenocytes¹¹⁶. Human flexor tendon cells treated with IL-1 β produced increased mRNA for cycloo-

genase-2, matrix metalloproteinase-1 (MMP-1), MMP-3, and PGE₂¹¹⁷. IL-1 β 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-1 β -mediated MMP-3 release, and use of fluoroquinolone is associated with tendon rupture and tendinopathy¹¹⁹⁻¹²¹. 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 enzymes¹²⁴, 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 remodeling¹²⁵⁻¹²⁷. 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 samples¹²⁹. Decreased MMP-3 and MMP-2 activity, but increased MMP-1 (collagenase-1) activity, has been reported in ruptured supraspinatus tendons¹³⁰. 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 activity¹³². 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 reported¹²⁵⁻¹³¹. 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 tendinopathy¹³³. 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 examination¹³⁴.

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 ruptures¹³⁸.

Various types of degeneration may be seen in tendons, but mucoid or lipid 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 lipid 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 occurs¹⁴²⁻¹⁴⁶. In rotator cuff tendinopathy, mucoid degeneration occurs, but fibrocartilaginous metaplasia, often accompanied by calcium deposition, is also common¹⁴⁷. Amyloid deposition in supraspinatus tendons with degenerative tears has also been reported¹⁴⁸.

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, occurs¹⁴⁹. 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 examination¹⁴⁹.

In samples from 397 ruptured Achilles tendons, Kannus and Jozsa found no evidence of inflammation under light and electron microscopy¹⁰. 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 rupture⁸⁷. In a recent study, immunohistochemical staining of neutrophils confirmed acute inflammation in all of sixty ruptured Achilles tendons¹⁵⁵. 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 painful¹⁴⁹. Pain may originate from a combination of mechanical and biochemical factors¹⁴⁹.

Tendon degeneration with mechanical breakdown of collagen could theoretically explain the pain, but clinical and surgical observations have challenged this view⁴⁹. 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 controls¹⁵⁶. Patients with chronic Achilles tendinopathy and patellar tendinopathy showed high concentrations of the neurotransmitter glutamate, with no significant elevation of the proinflammatory prostaglandin PGE₂¹⁵⁷. However, the levels of PGE₂ 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 neuro-modulator, and it is found in small unmyelinated sensory nerve fibers¹⁵⁸. 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 epicondylopathy¹⁵⁹⁻¹⁶². Sensory nerves transmit nociceptive information to the spinal cord, and increased levels of substance P correlate with pain levels in rotator cuff disease¹⁶².

An opioid system has been demonstrated in the Achilles tendons of rats¹⁶³. 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 cells¹⁶⁶. Tenocytes gradually migrate to the wound, and type-III collagen synthesis is initiated¹⁶⁷.

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 stage¹⁶⁷.

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 stage¹⁶⁸. 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 stress¹⁶⁹. A higher proportion of type-I collagen

is synthesized during this stage¹⁷⁰. 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 decline¹⁷².

Tendon healing can occur intrinsically, by proliferation of epitenon and endotenon tenocytes, or extrinsically, by invasion of cells from the surrounding sheath and synovium¹⁷³⁻¹⁷⁵. Epitenon tenoblasts initiate the repair process through proliferation and migration¹⁷⁶⁻¹⁷⁹. 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 cells¹⁸². 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 later¹⁸³⁻¹⁸⁷. 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 place¹⁸⁸.

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 preserved¹⁹¹. In extrinsic healing, scar tissue results in adhesion formation, which disrupts tendon gliding¹⁹². Different healing patterns may predominate in particular locations; for example, extrinsic healing tends to prevail in torn rotator cuffs¹⁹³.

MMPs are important regulators of extracellular matrix network remodeling, and their levels are altered during tendon healing¹²⁶⁻¹²⁸. 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 day¹⁹⁴. 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 cells¹⁹⁵⁻²⁰⁰. 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-

tion²⁰³⁻²⁰⁵. 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 tendons²⁰⁶. In that study, inhibition of nitric oxide synthase reduced healing, resulted in a decreased cross-sectional area, and reduced failure load²⁰⁶. 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 synthase²⁰⁷. 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 day²⁰⁷.

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 synthase²⁰⁸. 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 extravasation²⁰⁹⁻²¹¹. 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 problem²¹⁴. 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 months²¹⁵. 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 VEGF²¹⁶. Extracorporeal shock wave therapy promoted healing of experimental Achilles tendinopathy in rats²¹⁷. 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- β 1 (TGF- β 1) in the early stage and persistently elevated levels of IGF-1²¹⁷. 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/mm²) or sham treatment monthly for three months²¹⁸. 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 rabbits²²⁰.

Pulsed magnetic fields with a frequency of 17 Hz improved collagen fiber alignment in a rat Achilles tendinopathy model²²¹. In another study, tenotomized rat Achilles tendons were sutured and then treated with low-intensity galvanic current for fifteen minutes a day for two weeks²²². 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 formation²²³. 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

surgery²²⁴. 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 repair²²⁵. 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 controls²²⁶.

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 tendons²²⁷. 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 origin²²⁷. 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- β 2 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- β 1 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 tendons²³². The use of cytokines and growth factors to enhance tendon healing remains largely experimental and has been restricted to in vitro studies and animal models²³³⁻²⁴⁹. 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 non-viral vectors or direct gene transfer^{250,251}. Gene therapy enables the delivery of individual proteins to specific tissues and cells²⁵².

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 tendons²⁵³. 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 groups²⁵⁶. 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-7²⁵⁷. BMP-12 increases the expression of procollagen type-I and III genes in human patellar tenocytes, and it is found at sites of tendon remodeling²⁵⁸. 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 weeks²⁵⁹.

Transfer of genes to tendons is feasible, and, as the healing environment can be manipulated for up to eight to ten weeks²²⁶, 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 tendinopathy²⁵⁷⁻²⁶⁷; 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 vessels²⁶⁹. 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 genes²⁷⁰. However, MyoD may not be the only transcription factor responsible for myogenic differentiation; Myf5, myogenin, and MRF4 may also play a role²⁷¹. Transcription factors that regulate adipogenic and osteogenic differentiation have also been identified, but no transcription factors regulating tenocyte differentiation have yet been identified²⁷²⁻²⁷⁵.

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 regions²⁷⁶⁻²⁷⁹.

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 trauma²⁸². 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 junctions²⁸⁵. The fibronexus is presumed to transfer tensile forces to the extracellular matrix network²⁸⁶. 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 adhesions²⁸⁷.

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 used²⁸⁸⁻²⁹¹. Hyaluronate is found in synovial fluid around tendon sheaths²⁹². 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 model²⁹⁵. 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 synthesis²⁹⁶. 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 minutes²⁹⁸. 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.

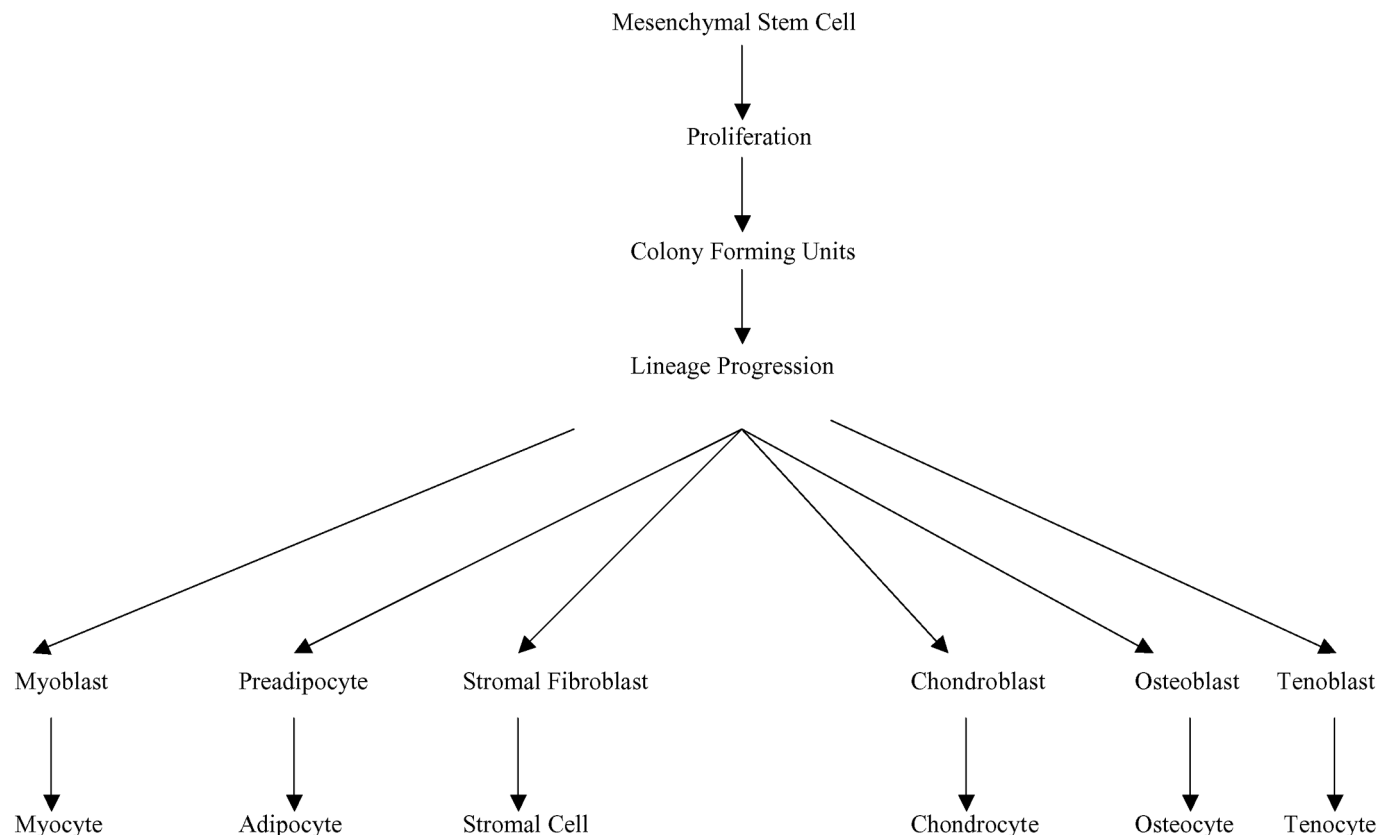


Fig. 3

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 tenocytes³⁰⁰. 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 subjects³⁰¹. 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 normal³⁰².

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 samples³⁰³. **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 slowly³⁰¹.

After the inflammatory phase of healing, controlled stretching is likely to increase collagen synthesis and improve fiber alignment, resulting in higher tensile strength³⁰⁶. Collagen that remains unstressed during the proliferative and remodeling phases remains haphazard in organization and is weaker than stressed collagen³⁰⁷. 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 tenocytes³⁰⁸.** Even fifteen minutes of cyclic biaxial mechanical strain applied to human tenocytes results in cellular proliferation³⁰⁹. Application of a cyclic load to wounded avian flexor tendons results in migration of epitenon cells into the wound³¹⁰. In rabbit patellar tendons, application of a 4% strain provides pro-

tection against degradation by bacterial collagenase³¹¹.

Clinical studies have shown the benefit of early mobilization following tendon repair, and several postoperative mobilization protocols have been advocated³¹²⁻³¹⁶. 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* models³¹⁷.

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.

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