Basic biology of tendon injury and healing

P. Sharma[1]
N. Maffulli[2]
[1]*Salisbury District Hospital, Wessex Deanery, UK*
[2]*Department of Trauma and Orthopaedic Surgery, Keele University School of Medicine, Stoke-on-Trent, UK*

Correspondence to: N. Maffulli
North Staffordshire Hospital, Thornburrow Drive, Hartshill, Stoke-on-Trent ST4 7QB
Email: n.maffulli@keele.ac.uk

Tendon disorders are commonly seen in clinical practice. Their successful treatment is difficult and patients often experience symptoms for prolonged periods of time. At present the aetiology of tendon disorders remains unclear, with several factors having been implicated. An improved understanding of tendon injury and healing is essential to enable focused treatment strategies to be devised
Keywords: Tendon, healing, growth factors, tissue engineering
Surgeon, 1 October 2005 309-316

INTRODUCTION

Tendons, by connecting muscle to bone, allow transmission of forces generated by muscle to bone resulting in joint movement. Tendon injuries may produce much morbidity and prolonged disability despite appropriate management.[1] Chronic overuse tendon problems probably account for 30% of all running related injuries, and the prevalence of elbow tendinopathy in tennis players can be as high as 40%.[2,3] The basic cell biology of tendons is still not fully understood and the treatment of tendon injury poses a considerable challenge for clinicians. This article describes the function and structure of tendons, reviews some aspects of tendon healing and injury, and reports on possible strategies for optimizing tendon healing and repair.

TENDON STRUCTURE

Healthy tendons are brilliant white and have a fibroelastic texture. Tendons can be rounded cords, strap-like bands or flattened ribbons.[4] Tenoblasts and tenocytes lie within the extracellular matrix network and constitute about 90% to 95% of the cellular elements of tendons.[5] The remaining 5% to 10% 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, and synthesize collagen and all components of the extracellular matrix.[6] All three pathways of energy generation, the aerobic Krebs cycle, anaerobic glycolysis and the pentose phosphate shunt, are present in human tenocytes.[7,8] With increasing age, metabolic pathways shift from aerobic to more anaerobic energy production.[9,10]

Tendons and ligaments have 7.5 times lower oxygen consumption compared with 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 ischaemia 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. 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 fibres along the long axis of the tendon.[16]

Soluble tropocollagen molecules form cross-links to create insoluble collagen molecules which aggregate to form collagen fibrils. 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 (Figure 1).[17-19] A collagen fibre is the smallest tendon unit which can be mechanically tested and is visible on light microscopy. Although collagen fibres are mainly oriented longitudinally, fibres also run transversely and horizontally, forming spirals and plaits.[20-22]

The ground substance of the extracellular matrix, which surrounds the collagen and the tenocytes, is composed of proteoglycans, glycosaminoglycans (GAG), glycoproteins and several other small molecules.[5] Proteoglycans are strongly hydrophilic, enabling

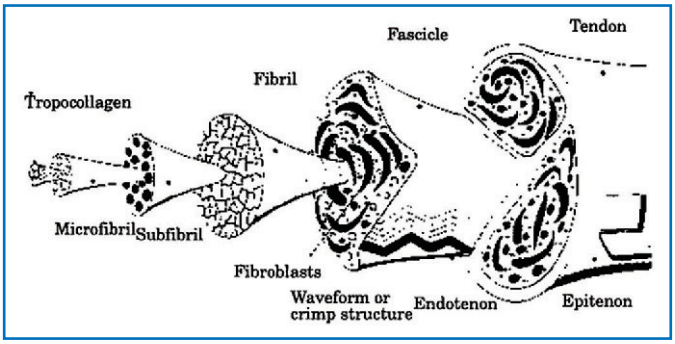

Figure 1: *Microscopic structure of tendon.*

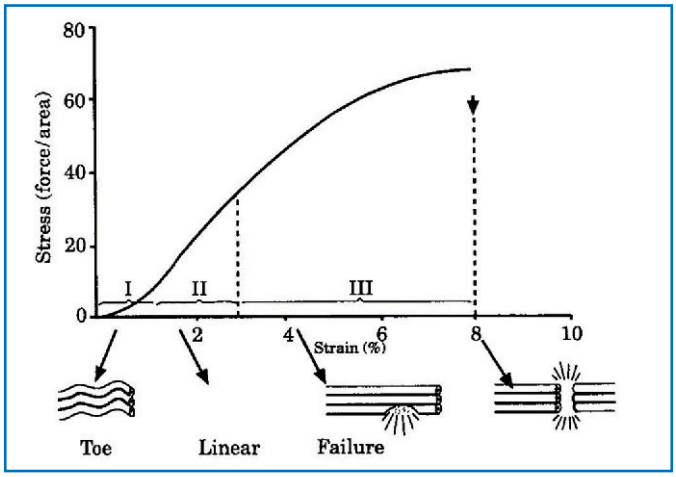

Figure 2: *Stress – strain curve of tendon.*

rapid diffusion of water soluble molecules and migration of cells. Adhesive glycoproteins, such as fibronectin and thrombospondin, participate in repair and regeneration processes in tendon.[20,23,24]

The epitenon is a fine, loose connective-tissue sheath containing the vascular, lymphatic and nerve supply to the tendon. It 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 fibre.[25,26] Superficially, the epitenon is surrounded by paratenon, a loose areolar connective tissue consisting of type I and III collagen fibrils, some elastic fibrils, and an inner lining of synovial cells.[9] Synovial tendon sheaths are present in areas subjected to increased mechanical stress, such as tendons of the hands and feet, where very 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]

At the myotendinous junction (MTJ), tendinous collagen fibrils are inserted into deep recesses formed by myocyte processes, allowing tension generated by intracellular contractile proteins of muscle fibres to be transmitted to the collagen fibrils.[27-31] This complex architecture reduces the tensile stress exerted on the tendon during muscle contraction.[27] However, the MTJ still remains the weakest point of the muscle-tendon unit.[27,31-34]

The osteotendinous junction (OTJ) is composed of four zones: a dense tendon zone, fibrocartilage, mineralized fibrocartilage, and bone.[35] The specialized structure of the OTJ prevents collagen fibre bending, fraying, shearing and failure.[36,37]

BLOOD SUPPLY

Tendons receive their blood supply from three main sources: the intrinsic systems at the MTJ and OTJ, and from the extrinsic system via the paratenon or the synovial sheath.[38,39] The ratio of blood supply from the intrinsic to extrinsic systems 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.[40,41] At the MTJ, perimyseal vessels from the muscle continue between the fasciculi of the tendon.[25] However, blood vessels originating from the muscle are unlikely to extend beyond the proximal third of the tendon.[38] The blood supply from the OTJ is sparse and limited to the insertion zone of the tendon, although vessels from the extrinsic system communicate with periosteal vessels at the OTJ.[5,38]

In tendons with sheaths, branches from major vessels pass through the vincula (mesotenon) to reach the visceral sheet of the synovial sheath, where they form a plexus.[18] This plexus supplies the superficial part of the tendon, while some vessels from the vinculae penetrate the epitenon. These vessels run in the endotenon septae, and form a connection between the peri- and intra-tendinous vascular networks.

In the absence of a synovial sheath, the paratenon provides the extrinsic component of the vasculature. Vessels entering the paratenon run transversely and branch repeatedly to form a complex vascular network.[42] Arterial branches from the paratenon penetrate the epitenon to run in the endotenon septae, where an intratendinous vascular network with abundant anastomoses is formed.[5,43]

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 2cm to 7cm proximal to the tendon insertion.[38,44]. However, laser Doppler flowmetry has demonstrated substantially reduced blood flow near the Achilles tendon insertion, with an otherwise even blood flow throughout the tendon.[45] A similar zone of hypovascularity is present on the dorsal surface of the flexor digitorum profundus tendon subjacent to the volar plate, within 1cm of the tendon insertion.[46] In general, tendon blood flow declines with increasing age and mechanical loading.[45]

BIOMECHANICS

Tendons not only transmit force generated by muscle to bone, but they act as buffers by absorbing external forces to limit muscle damage.[47] Tendons exhibit high mechanical strength, good flexibility, and an optimal level of elasticity to perform their unique role.[16,48,49] Tendons are viscoelastic tissues which display stress relaxation and creep.[50,51]

A stress-strain curve helps to demonstrate the behaviour of tendon (Figure 2). At rest, collagen fibres and fibrils display a crimped configuration.[52] If the strain remains below 4%, tendon behaves in an elastic fashion and returns to its original length when unloaded.[53] Microscopic failure occurs when the strain exceeds 4%, and beyond 8% to 10% strain macroscopic failure occurs due to intrafibril damage by molecular slippage.[48,54,55] After this, complete failure occurs rapidly and the fibres recoil into a tangled bud at the ruptured end.[47]

© 2005 Surgeon 3: 5; 309-316

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. Overuse injuries generally have a multifactorial origin. In chronic tendon disorders, interaction between intrinsic and extrinsic factors is common.[12]

The label 'tendinosis' has been in use for more than two decades to describe collagen degeneration in tendinopathy.[56] Despite that, most clinicians still use the term "tendonitis" or "tendinitis", 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 suggest that the terms tendinosis, tendonitis and tendinitis only be used after histopathological examination.[57]

Excessive loading of tendons during vigorous physical training is regarded as the main pathological stimulus for degeneration.[58] Tendons respond to repetitive overload beyond physiological threshold by either inflammation of their sheath, degeneration of their body, or a combination of both.[59] It remains unclear whether different stresses induce different responses. Active repair of fatigue damage must occur, or tendons would weaken and eventually rupture.[60] The repair mechanism is probably mediated by resident tenocytes, which continually monitor the extracellular matrix. Failure to adapt to recurrent excessive loads results in the release of cytokines leading to further modulation of cell activity.[61] Tendon damage may even occur from stresses within physiological limits, as frequent cumulative microtrauma may not allow enough time for repair.[58] Microtrauma can also result from non-uniform stress within tendons, producing abnormal load concentrations and frictional forces between the fibrils, resulting in localised fibre damage.[62]

The aetiology of tendinopathy remains unclear, and many factors have been implicated.[17,63] Ischaemia occurs when a tendon is under maximal tensile load. Upon relaxation, reperfusion occurs, generating oxygen free radicals.[64,65] These oxygen free radicals may result in damage to the tendon. Human tenocytes express peroxiredoxin 5, a peroxidase which forms part of the body's antioxidant defences. Peroxiredoxin 5 is upregulated in tendinopathic tendons, supporting the view that oxidative stress plays a role in tendinopathy.[65,66]

Hypoxia may also play a role, as tendons rely on oxidative energy metabolism to maintain cellular ATP levels.[67] During locomotion, tendons store energy, 5% to 10% of which is converted into heat.[68,69] In the equine superficial digital flexor tendon, temperatures up to 45^{0}C have been recorded during galloping.[70] Although short periods at 45^{0}C are unlikely to result in tenocyte death, repeated hyperthermic insults and prolonged durations of exposure may compromise cell viability and produce tendon degeneration.[71,72]

Impaired tenocyte apoptosis has been implicated in rotator cuff tendinopathy.[73] An increased number of apoptotic cells are present in ruptured supraspinatus tendons compared with normal subscapularis tendons.[74] Degenerate quadriceps femoris tendons exhibited a 1.6 times greater rate of spontaneous apoptosis than normal tendons.[75]

In animal studies, local administration of cytokines and inflammatory prostaglandins has resulted in tendinopathy.[75,76] Application of strain to human patellar tenocytes, cultured on a microgrooved silicone membrane, resulted in increased prostaglandin E_2 production.[77] Thus, repetitive strain may be the initiator of tendon injury by stimulating the production of inflammatory substances.

Although ciprofloxacin reduces prostaglandin E_2 (PGE_2) release, fluoroquinolones have been implicated in the pathogenesis of tendinopathy.[79] This may be because ciprofloxacin interacts with cytokines leading to enhanced interleukin-1 mediated matrix metalloproteinase 3 (MMP3) release, inhibits fibroblast metabolism causing reduced cell proliferation and reduces collagen and matrix synthesis.[80,81]

Several studies have demonstrated an alteration in the levels of MMPs in tendinopathy. Matrix metalloproteinases are proteolytic enzymes that are responsible for degrading components of the extracellular matrix. Down-regulation of MMP 3 mRNA in tendinopathic Achilles tendon, along with up-regulation of MMP 2 and vasculoendothelial growth factor (VEGF), have been reported in Achilles tendinopathy.[82,83] In ruptured supraspinatus tendons, increased MMP 1, and reduced MMP 2 and MMP 3 activity were observed.[84] However, in a rabbit model of supraspinatus tears, increased expression of MMP 2 and TIMP-1 (tissue inhibitor of metalloproteinase 1) was noted.[85] Human flexor tendon cells treated with interleukin-1 produced increased mRNA for cyclo-oxygenase 2, MMP 1, MMP 3, and PGE_2.[86] Changes in MMP level may follow a temporal sequence and may also vary between different sites in the body.

Failure to adapt to recurrent excessive loads may result in release of cytokines by tenocytes, leading to further modulation of cell activity.[61] An increase in cytokine levels in response to repeated injury or mechanical strain may induce MMP release, with degradation of the extracellular matrix, and eventually tendinopathy.

The aetiology of tendon rupture still remains unclear.[12] Degenerative tendinopathy is the most common histological finding in spontaneous tendon ruptures. Arner *et al* (1959) first reported degenerative changes in all their 74 patients with Achilles tendon rupture, and postulated that these changes were primary abnormalities present before the rupture.[87] Kannus and Jozsa (1991) found degenerative changes in 865 of 891 (97%) spontaneous tendon ruptures, whilst degenerative changes were only seen in 149 of 445 (34%) of control tendons.[10] Tendon degeneration may lead to reduced tensile strength and a predisposition to rupture. Indeed, ruptured Achilles tendons are more degenerate than tendinopathic tendons.[88]

HISTOLOGICAL CHANGES

Tendinosis can be viewed as a failure of cell matrix adaptation to trauma due to an imbalance between matrix degeneration and synthesis.[58,61] Macroscopically, the affected portions of the tendon lose their normal glistening white appearance and become grey-brown and amorphous. Tendon thickening, which can be diffuse, fusiform or nodular, occurs.[89]

Histologically, tendinopathy is characterised by an absence of inflammatory cells and a poor healing response, with non-inflammatory intratendinous collagen degeneration, fibre disorientation and thinning, hypercellularity, scattered vascular ingrowth, and increased interfibrillar glycosaminoglycans.[18,90-92] Frank inflammatory lesions and granulation tissue are infrequent and are mostly associated with tendon ruptures.[93]

Tendinosis is often clinically silent, and its only manifesta-

tion may be a rupture, but it may also coexist with symptomatic paratendinopathy.[65,94] The general pattern of intratendinous degeneration is common to ruptured and tendinopathic tendons, with a greater degree of degeneration seen in ruptured tendons.[88]

PAIN IN TENDINOPATHY

The mechanism causing pain in tendinopathy is not fully understood. Typically, pain was attributed to inflammation. However, chronically painful Achilles tendons have no evidence of inflammation, and many tendons with intratendinous pathology detected on magnetic resonance imaging (MRI) or ultrasound are not painful.[95] As tendinopathies are degenerative but not inflammatory conditions, recently it has been proposed that pain may originate from a combination of mechanical and biochemical causes.[95] Tendon degeneration with mechanical breakdown of collagen could explain the pain, but clinical and surgical observations challenge this view.[95] Chemical irritants and neurotransmitters may generate pain in tendinopathy. Microdialysis sampling revealed a twofold increase in lactate levels in tendinopathic tendons compared with controls.[96] High concentrations of the neurotransmitter glutamate with no abnormal elevation of the pro-inflammatory prostaglandin PGE_2 have also been found in patients with Achilles tendinopathy and patellar tendinopathy.[97]

TENDON HEALING

Tendon healing studies have predominantly been performed on transected animal tendons or ruptured human tendons, and their relevance to degenerate 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 24 hours monocytes and macrophages predominate and phagocytosis of necrotic materials occurs. Vasoactive and chemotactic factors are released, leading to increased vascular permeability, initiation of angiogenesis, stimulation of tenocyte proliferation, and recruitment of more inflammatory cells.[98,99] Tenocytes gradually migrate to the wound, and type III collagen synthesis is initiated.[100]

After a few days, the regenerative stage begins. Synthesis of type III collagen peaks during this stage, which lasts for a few weeks. Water content and glycosaminoglycan concentrations remain high during this stage.[100]

After approximately six weeks, the remodelling stage commences, with decreased cellularity and decreased collagen and glycosaminoglycan synthesis. The remodelling phase can be divided into a consolidation and a maturation stage.[101] The consolidation stage commences at about six weeks and continues 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 fibres become aligned in the direction of stress.[102] A higher proportion of type I collagen is synthesized during this stage.[103] After ten weeks, the maturation stage occurs, with gradual change of fibrous tissue to scar-like tendon tissue.[102,104] The maturation stage continues for up to a year. However, during the latter half of this stage tenocyte metabolism and tendon vascularity decline.[105]

Epitenon tenoblasts initiate the repair process through proliferation and migration.[105-109] Healing in severed tendons can be performed by cells from the epitenon alone, without relying on adhesions for vascularity or cellular support.[110,111] Internal tenocytes contribute to the intrinsic repair process and secrete larger and more mature collagen than epitenon cells.[112] Despite this, both epitenon and tendon fibroblasts synthesize collagen during repair, and different cells probably produce collagen at different time points. Initially, collagen is produced by epitenon cells with endotenon cells synthesizing collagen later.[113-117] The relative contribution of each cell type may be influenced by the type of trauma sustained, anatomical position, presence of a synovial sheath, and the amount of post-repair motion stress.[118] Tenocyte function may vary depending on the region of origin. Cells from the tendon sheath produce less collagen and GAG compared with epitenon and endotenon cells. However, flexor tendon sheath cells proliferate more rapidly.[119,120] 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 improved biomechanics and less complications. In particular, a normal gliding mechanism within the tendon sheath is preserved.[121] In extrinsic healing, scar tissue results in adhesion formation which disrupts tendon gliding.[122] Different healing patterns may predominate in particular locations, and extrinsic healing prevails in torn rotator cuffs.[123]

MMPs are important regulators of extracellular matrix remodelling, and their levels are altered during tendon healing.[124-126] In a rat flexor tendon laceration model, the expression of MMP-9 and MMP-13 (Collagenase-3) peaked between days seven and 14. MMP-2, MMP-3, and MMP-14 (MT1-MMP) levels increased after surgery, and remained high until day 28.[127] It appears that MMP-9 and MMP-13 participate only in collagen degradation, whereas MMP-2, MMP-3 and MMP-14 participate not only in collagen degradation but also in collagen remodelling. Cytokines are small proteins which evoke cellular responses by engaging specific cell surface receptors.[128] A complex system exists, where cytokines may have multiple dose-dependent effects, and act synergistically with other cytokines. Growth factors act as regulators of the phases of tendon healing.[128-133] Wounding and inflammation provoke release of growth factors from platelets, polymorphonuclear leukocytes, and macrophages.[129,130,133] These growth factors induce neovascularization and chemotaxis for fibroblasts and for stimulating fibroblast proliferation and synthesis of collagen.[134,135]

LIMITATIONS OF HEALING

Adhesion formation after intrasynovial tendon injury poses a major clinical problem.[136] Synovial sheath disruption at the time of 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 tissues to attach to the repair site resulting in adhesion formation.

Despite remodelling, the biochemical and mechanical properties of healed tendon tissue never match those of intact tendon. In spontaneously healed transected sheep Achilles tendons, rupture force was only 56.7% of normal at 12 months.[137] One possible reason for this may be the absence of mechanical loading during the period of immobilization.[138]

CONCLUSION

Tendon injuries give rise to significant morbidity, and at present only limited scientifically proven management modalities exist. A better understanding of tendon function and healing will allow specific and more effective treatment strategies to be developed.[138]

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**(3):157-61.
2. James SL, Bates BT, Osternig LR. Injuries to runners. *Am J Sports Med* 1978;**6**(2):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**(4):234-38.
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: American academy of orthopaedic surgeons; 1995:185-203.
5. Kannus P, Jozsa, L, Jarvinnen M. Basic science of tendons. In: Garrett WJ, Speer K, Kirkendall DT, Editors. Principles and practice of orthopaedic sports medicine. Philadelphia: Lippincott Williams and Wilkins; 2000:21-37.
6. O'Brien M. Structure and metabolism of tendons. Scand J Med Sci Sports. 1997;7(2):55-61.
7. Jozsa L, Balint JB, Reffy A, Demel Z. Histochemical and ultrastructural study of adult human tendon. *Acta Histochemica* 1979;65(2):250-57.
8. Kvist M, Jozsa L, Jarvinen M, Kvist H. Chronic Achilles paratenonitis in athletes: a histological and histochemical study. *Pathology* 1987;**19**:1.
9. Kvist M, Jozsa L, Jarvinen M, Kvist H. Fine structural alterations in chronic Achilles paratenonitis in athletes. *Pathol Res Pract* 1985;**180**(4):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**(10):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**(4): 542-46.
12. Williams JG. Achilles tendon lesions in sport. *Sports Med* 1986;**3**(2):114-35.
13. Hess GP, Cappiello WL, Poole RM, Hunter SC. Prevention and treatment of overuse tendon injuries. *Sports Med* 1989;**8**(6):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**(4):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**(3):165-75.
16. Kirkendall DT, Garrett WE. Function and biomechanics of tendons. *Scand J Med Sci Sports* 1997;7(2):62-66.
17. Astrom M. On the nature and etiology of chronic achilles tendinopathy. [PhD Thesis]. Lund University, Sweden 1997.
18. Jozsa L KP. Human Tendon: anatomy, physiology and pathology Champaign: 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**(5):311-17.
20. Jozsa L, Kannus P, Balint JB, Reffy A. Three-dimensional ultrastructure of human tendons. *Acta Anat (Basel)* 1991;**142**(4):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**(4):293-99.
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**(5):1197-209.
24. Miller RR, McDevitt CA. Thrombospondin in ligament, meniscus and intervertebral disc. *Biochim Biophys Acta* 1991;**1115**(1):85-88.
25. Elliott D. Structure and function of mammalian tendon. *Biol Rev* 1965;**40**:392.
26. Kastelic J, Galeski A, Baer E. The multicomposite structure of tendon. *Connect Tissue Res* 1978;**6**(1):11-23.
27. 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**(3):199-205.
28. Michna H. A peculiar myofibrillar pattern in the murine muscle-tendon junction. *Cell Tissue Res* 1983;**233**(1):227-31.
29. Trotter JA, Baca JM. A stereological comparison of the muscle-tendon junctions of fast and slow fibers in the chicken. *Anat Rec* 1987;**218**(3):256-66.
30. Tidball JG. Myotendinous junction of tonic muscle cells: structure and loading. *Cell Tissue Res* 1986;**245**:315.
31. Tidball JG. Myotendinous junction injury in relation to junction structure and molecular composition. *Exerc Sport Sci Rev* 1991;**19**:419-45.
32. 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.
33. Garrett WE. Muscle strain injuries: clinical and basic aspects. *Med Sci Sports Exerc* 1990;**22**(4):436-43.
34. Jarvinen M, Kannus P, Kvist M, Isola J, Lehto M, Jozsa L. Macromolecular composition of the myotendinous junction. *Exp Mol Pathol* 1991;**55**(3):230-37.
35. Benjamin M, Ralphs JR. Fibrocartilage in tendons and ligaments-an adaptation to compressive load. *J Anat* 1998;**193** (Pt 4):481-94.
36. Benjamin M, Qin S, Ralphs JR. Fibrocartilage associated with human tendons and their pulleys. *J Anat* 1995;**187** (Pt 3):625-33.
37. 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.
38. Carr AJ, Norris SH. The blood supply of the calcaneal tendon. *J Bone Joint Surg Br* 1989;**71**(1):100-1.

39. 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**(3):359-64.
40. Kvist M, Jozsa L, Jarvinen M. Vascular changes in the ruptured Achilles tendon and paratenon. *Int Orthop* 1992;**16**(4):377-82.
41. Naito M, Ogata K. The blood supply of the tendon with a paratenon. An experimental study using hydrogen washout technique. *Hand* 1983;**15**(1):9-14.
42. Reynolds NL, Worrell TW. Chronic Achilles peritendinitis: etiology, pathophysiology, and treatment. *J Orthop Sports Phys Ther* 1991;**13**:1716.
43. Field PL. Tendon fibre arrangement and blood supply. *Aust N Z J Surg* 1971;**40**(3):298-302.
44. Niculescu V, Matusz P. The clinical importance of the calcaneal tendon vasculature (tendo calcaneus). *Morphol Embryol (Bucur)* 1988;**34**(1):5-8.
45. Astrom M. Laser Doppler flowmetry in the assessment of tendon blood flow. *Scand J Med Sci Sports* 2000;**10**(6):365-67.
46. 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**(5):806-12.
47. Best TM, Garrett WE. Basic science of soft tissue: muscle and tendon. In: DeLee JC DD, Editors. Orthopaedic sports medicine. Philadelphia: WB Saunders; 1994:1.
48. O' Brien M. Functional anatomy and physiology of tendons *Clin Sports Med* 1992;**11**:505.
49. Oxlund H. Relationships between the biomechanical properties, composition and molecular structure of connective tissues. *Con Tis Res* 1986;**15**(1-2):65-72.
50. Carlstedt CA, Nordin M. Biomechanics of tendons and ligaments. In: Nordin M FV, Editors. Basic biomechanics of the musculoskeletal system. Philadelphia: Lea and Ferbiger; 1989:59-74.
51. Viidik A. Tendons and ligaments. In: W C, Editors. Extracellular Matrix. Vol. 1. Amsterdam: Harwood academic publishers; 1996:303-327.
52. Diamant J, Keller A, Baer E, Litt M, Arridge RG. Collagen; ultrastructure and its relation to mechanical properties as a function of ageing. Proceedings of the Royal Society of London. Series B: Biological Sciences. 1972;180(60):293-315.
53. Curwin SL, Stanish WD. Tendinitis: its etiology and treatment Lexington: Collamore press; 1984.
54. Butler DL, Grood ES, Noyes FR, Zernicke RF. Biomechanics of ligaments and tendons. *Exer Sport Sci Rev* 1978;**6**:125-81.
55. Kastelic J, Baer E. Deformation in tendon collagen. *Symp Soc Exp Biol* 1980;**34**:397-435.
56. Puddu G, Ippolito E, Postacchini F. A classification of Achilles tendon disease. *Am J Sports Med* 1976;**4**(4):145-50.
57. Maffulli N, Khan KM, Puddu G. Overuse tendon conditions: time to change a confusing terminology. *Arthroscopy* 1998;**14**(8):840-43.
58. Selvanetti A, Cipolla M, Puddu, G. Overuse tendon injuries: Basic science and classification. *Oper Tech Sports Med* 1997;**5**:110-17.
59. Benazzo F, Maffulli N. An operative approach to Achilles tendinopathy. *Sports Med Arthroscopy Rev* 2000;**8**:96-101.
60. 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**(4):987-1000.
61. Leadbetter WB. Cell-matrix response in tendon injury. *Clin Sports Med* 1992;**11**(3):533-78.
62. Arndt AN, Komi PV, Bruggemann GP, Lukkariniemi J. Individual muscle contributions to the in vivo achilles tendon force. *Clin Biomech* 1998;**13**(7):532-41.
63. Kvist M. Achilles Tendon Overuse Injuries. [PhD Thesis]. University of Turku, Finland;1991.
64. Goodship AE, Birch HL, Wilson AM. The pathobiology and repair of tendon and ligament injury. *Vet Clin North Am Equine Pract* 1994;**10**(2):323-49.
65. Bestwick CS, Maffulli N. Reactive oxygen species and tendon problems: review and hypothesis. *Sports Med Arthroscopy Rev* 2000;**8**:6-16.
66. 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**(3):667-73.
67. Birch HL, Rutter GA, Goodship AE. Oxidative energy metabolism in equine tendon cells. *Res Vet Sci* 1997;**62**(2): 93-97.
68. Ker RF. Dynamic tensile properties of the plantaris tendon of sheep (Ovis aries). *J Exp Biol* 1981;**93**:283-302.
69. Riemersma DJ, Schamhardt HC. In vitro mechanical properties of equine tendons in relation to cross-sectional area and collagen tendon. *Res Vet Sci* 1985;**39**:263-70.
70. Wilson AM, Goodship AE. Exercise-induced hyperthermia as a possible mechanism for tendon degeneration. *J Biomech* 1994;**27**(7):899-905.
71. Arancia G, Crateri Trovalusci P, Mariutti G, Mondovi B. Ultrastructural changes induced by hyperthermia in Chinese hamster V79 fibroblasts. *Int J Hyperthermia* 1989;**5**(3):341-50.
72. Birch HL, Wilson AM, Goodship AE. The effect of exercise-induced localised hyperthermia on tendon cell survival. *J Exp Biol* 1997;**200** (Pt 11):1703-8.
73. Yuan J, Wang MX, Murrell GA. Cell death and tendinopathy. *Clin Sports Med* 2003;**22**(4):693-701.
74. Yuan J, Murrell GA, Wei AQ, Wang MX. Apoptosis in rotator cuff tendonopathy. *J Orthop Res* 2002;**20**(6):1372-79.
75. 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**(5):R253-61.
76. 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**(2):168-77.
77. 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**(4):349-57.
78. 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**(3-4):128-33.
79. 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**(11):3034-40.
80. 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**(11):1306-10.
81. Williams RJ, Attia E, Wickiewicz TL, Hannafin JA. The effect of ciprofloxacin on tendon, paratenon, and capsular fibroblast metabolism. *Am J Sports Med* 2000;**28**(3):364-69.
82. 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**(3):159-69.
83. 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**(6):970-75.
84. 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**(2):185-95.
85. 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**(5):927-33.
86. 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**(2): 256-64.
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**(5-6):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**(12):1983-90.
89. Khan KM, Cook JL, Bonar F, Harcourt P, Astrom M. Histopathology of common tendinopathies. Update and implications for clinical management. *Sports Medicine* 1999;**27**(6):393-408.
90. Khan KM, Maffulli N. Tendinopathy: an Achilles' heel for athletes and clinicians. *Clin J Sport Med* 1998;**8**(3):151-54.
91. Movin T, Gad A, Reinholt FP, Rolf C. Tendon pathology in long-standing achillodynia. Biopsy findings in 40 patients. *Acta Orthop Scand* 1997;**68**(2):170-75.
92. Astrom M, Rausing A. Chronic Achilles tendinopathy. A survey of surgical and histopathologic findings. *Clin Orthop* 1995;**316**:151-64.
93. Maffulli N, Barrass V, Ewen SW. Light microscopic histology of achilles tendon ruptures. A comparison with unruptured tendons. *Am J Sports Med* 2000;**28**(6):857-63.
94. Kvist M. Achilles tendon injuries in athletes. *Ann Chir Gynaecol* 1991;**80**(2):188-201
95. Khan KM, Cook JL, Bonar F, Harcourt P, Astrom M. Histopathology of common tendinopathies. Update and implications for clinical management. *Sports Med* 1999;**27**(6): 393-408.
96. 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**(5):934-38.
97. 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**(6):378-81.
98. Murphy PG LB, 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.
99. Pierce GF, Mustoe TA, Lingelbach J, Masakowski VR, Griffin GL, Senior RM, Deuel TF. Platelet derived growth factor and transforming growth factor-b enhance tissue repair activities by unique mechanisms. *J Cell Biol* 1989;**109**:429-40.
100. Oakes BW. Tissue healing and repair: tendons and ligaments. In: Frontera WR. Editor. Rehabilitation of sports injuries: scientific basis. Oxford: Blackwell Science; 2003:56-98.
101. Tillman LJ, Chasan NP. Properties of dense connective tissue and wound healing. In: Hertling D, Kessler RM, Editors. Management of common musculoskeletal disorders. Philadelphia: Lippincott; 1996.
102. Hooley CJ, Cohen RE. A model for the creep behaviour of tendon. *Int J Biol Macromol* 1979;**1**:123-32.
103. 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.
104. Farkas LG, McCain WG, Sweeney P, Wilson W, Hurst LN, Lindsay WK. An experimental study of changes following silastic rod preparation of new tendon sheath and subsequent tendon grafting. *J Bone Joint Surg Am* 1973;**55**(6):149-58.
105. Amiel D, Akeson W, Harwood FL, Frank CB. Stress deprivation effect on metabolic turnover of medial collateral ligament collagen. *Clin Orthop* 1987;**172**:25-27.
106. 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**:551-58.
107. 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.
108. Manske PR, Gelberman RH, Lesker PA. Flexor tendon healing. *Hand Clin* 1985;**1**(1):25-34.
109. 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.
110. Gelberman RH, Manske PR, Akeson WH, Woo SL, Lundborg G, Amiel D. Flexor tendon repair. *J Orthop Res* 1986;**4**(1):119-28.
111. 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**:107-27.
112. 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**(4):326-33.
113. Ingraham JM, Hauck RM, Ehrlich HP. Is the tendon embryogenesis process resurrected during tendon healing? *Plast Reconstr Surg* 2003;**112**(3):844-54.
114. Lundborg G, Rank F. Experimental studies on cellular mechanisms involved in healing of animal and human flexor tendon in synovial environment. *Hand* 1980;**12**(1):3-11.
115. 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**(5):451-61.
116. Russell JE, Manske PR. Collagen synthesis during primate flexor tendon repair in vitro. *J Orthop Res* 1990;**8**(1):13-20.
117. Becker H, Graham MF, Cohen IK, Diegelmann RF. Intrinsic tendon cell proliferation in tissue culture. *J Hand Surg [Am]* 1981;**6**(6):616-19.
118. Koob TJ. Biomimetic approaches to tendon repair. *Comp Biochem Physiol A Mol Integr Physiol* 2002;**133**(4):1171-92.
119. 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**(5):847-54.
120. 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**(2):127-33.
121. Koob TJ, Summers AP. Tendon-bridging the gap. *Comp Biochem Physiol A Mol Integr Physiol* 2002;**133**(4):905-9.
122. Strickland JW. Flexor tendons: acute injuries. In: Green D, Hotchkiss R, Pedersen W. Editors. Green's operative hand surgery. New York: Churchill Livingstone; 1999:1851-1897.
123. Uhthoff HK, Sarkar K. Surgical repair of rotator cuff ruptures. The importance of the subacromial bursa. *J Bone Joint Surg Br* 1991;**73**(3):399-401.
124. Vu TH, Werb Z. Matrix metalloproteinases: effectors of development and normal physiology. *Genes Dev* 2000;**14**(17):2123-33.
125. Birkedal-Hansen H. Proteolytic remodeling of extracellular matrix. *Curr Opin Cell Biol* 1995;**7**(5):728-35.
126. 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**(3):159-69.
127. 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;b(5):814-23.
128. Evans CH. Cytokines and the role they play in the healing of ligaments and tendons. *Sports Med* 1999;**28**(2):71-76.
129. 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.
130. 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**(4):937-44.
131. Chang J MD, Thunder R, Mehraa 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**A:1052.
132. Woo SL, Hildebrand K, Watanabe N, Fenwick JA, Papageorgiou CD, Wang JH. Tissue engineering of ligaments and tendon healing. *Clin Orthop* 1999;**367**:S312-23.
133. Natsuume 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.
134. 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.
135. 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**(3):370-76.
136. Manske PR. Flexor tendon healing. *J Hand Surg [Br]* 1988;**13**(3):237-45.
137. 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**(6):364-69.
138. Sharma P, Maffulli N. Tendon injury and tendinopathy: healing and repair. *J Bone Joint Surg Am* 2005;**87**-A(1):187-202.

TRUE OR FALSE QUESTIONS (Answers at end of issue)

With regard to tendon structure:

- Collagen type I accounts for about 65-80% of the dry mass
- Tendon cells have a very high metabolic rate
- All tendons are surrounded by a synovial sheath
- The musculotendinous junction is the weakest point of the muscle-tendon unit
- Tendon vascularity is compromised at sites of torsion or compression

Tendon healing:

- Occurs in three overlapping phases
- Commences with the regenerative phase
- Is modulated by cytokines and growth factors
- Results in collagen type III production in the early stages
- When complete, results in healed tendon on normal tensile strength

© 2005 Surgeon 3: 5; 309-316