Basic biology of tendon injury and healing

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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
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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

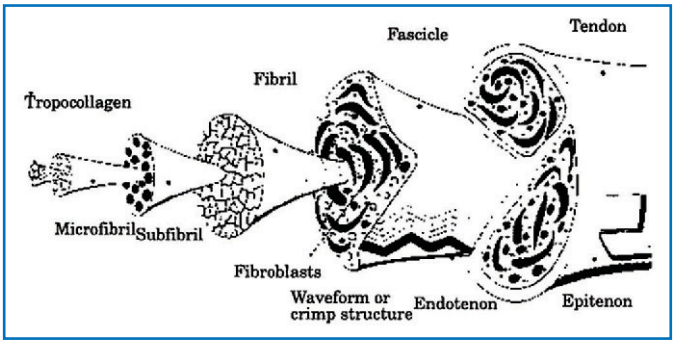

Figure 1: *Microscopic structure of tendon.*

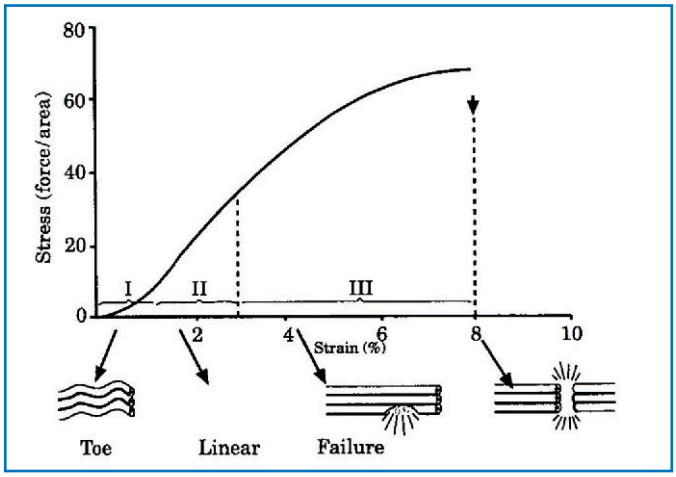

Figure 2: *Stress – strain curve of tendon.*

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]

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